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ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non –ST-Elevation Myocardial Infarction :

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ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction)

Developed in Collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine

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Preamble

It is important that the medical profession play a significant role in critically evaluating the use of diagnostic procedures and therapies in the detection, management, or prevention of disease states. Rigorous and expert analysis of the available data documenting absolute and relative benefits and risks of those procedures and therapies can produce helpful guidelines that improve the effectiveness of care, optimize patient outcomes, and favorably affect the overall cost of care by focusing resources on the most effective strategies.

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have jointly engaged in the production of such guidelines in the area of cardiovascular disease since 1980. The American College of Cardiology (ACC)/AHA Task Force on Practice Guidelines, whose charge is to develop, update, or revise practice guidelines for important cardiovascular diseases and procedures, directs this effort. Writing committees are charged with the task of performing an assessment of the evidence and acting as an independent group of authors to develop, update, or revise written recommendations for clinical practice.

Experts in the subject under consideration have been selected from both organizations to examine subject-specific data and write guidelines. The process includes additional representatives from other medical practitioner and specialty groups when appropriate. Writing committees are specifically charged to perform a formal literature review, weigh the strength of evidence for or against a particular treatment or procedure, and include estimates of expected health

outcomes where data exist. Patient-specific modifiers, comorbidities, and issues of patient preference that might influence the choice of particular tests or therapies are considered, as well as frequency of follow-up and cost effectiveness. When available, information from studies on cost will be considered; however, review of data on efficacy and clinical outcomes will constitute the primary basis for preparing recommendations in these guidelines.

The ACC/AHA Task Force on Practice Guidelines makes every effort to avoid any actual, potential, or perceived conflict of interest that may arise as a result of an industry relationship or personal interest of a member of the Writing Committee. Specifically, all members of the Writing Committee, as well as peer reviewers of the document, were asked to provide disclosure statements of all such relationships that may be perceived as real or potential conflicts of interest. Writing Committee members are also strongly encouraged to declare a previous relationship with industry that may be perceived as relevant to guideline development. If a Writing Committee member develops a new relationship with industry during their tenure, they are required to notify guideline staff in writing. The continued participation of the Writing Committee member will be reviewed. These statements are reviewed by the parent task force, reported orally to all members of the Writing Committee at each meeting, and updated and reviewed by the Writing Committee as changes occur. Please refer to the methodology manual for ACC/AHA Guideline Writing Committees further description of relationships with industry policy, available on the ACC and AHA World Wide Web sites (http://www.acc.org/qualityandscience/clinical/manual/manual%5Fi.htm and http://www.circ.ahajournals.org/manual/). See Appendix 1 for a list of Writing Committee member relationships with industry and Appendix 2 for a listing of peer reviewer relationships with industry that are pertinent to this guideline.

These practice guidelines are intended to assist health care providers in clinical decision making by describing a range of generally acceptable approaches for the diagnosis, management, and prevention of specific diseases or conditions. Clinical decision making should consider the quality and availability of expertise in the area where care is provided. These guidelines attempt to define practices that meet the needs of most patients in most circumstances. These guideline recommendations reflect a consensus of expert opinion after a thorough review of the available, current scientific evidence and are intended to improve patient care.

Patient adherence to prescribed and agreed upon medical regimens and lifestyles is an important aspect of treatment. Prescribed courses of treatment in accordance with these recommendations will only be effective if they are followed. Since lack of patient understanding and adherence may adversely affect treatment outcomes, physicians and other health care providers should make every effort to engage the patient in active participation with prescribed medical regimens and lifestyles.

If these guidelines are used as the basis for regulatory/payer decisions, the ultimate goal is quality of care and serving the patient's best interests. The ultimate judgment regarding care of a particular patient must be made by the health care provider and patient in light of all the circumstances presented by that patient. There are circumstances in which deviations from these guidelines are appropriate.

The guidelines will be reviewed annually by the ACC/AHA Task Force on Practice Guidelines and will be considered current unless they are updated, revised, or sunsetted and withdrawn from distribution. The executive summary and recommendations are published in the August 7, 2007, issue of the *Journal of the American College of Cardiology* and August 7, 2007, issue of *Circulation*. The full- text guidelines are e-published in the same issue of the journals noted above, as well as posted on the ACC (www.acc.org) and AHA (www.americanheart.org) World Wide Web sites. Copies of the full text and the executive summary are available from both organizations.

Sidney C. Smith, Jr, MD, FACC, FAHA
Chair, ACC/AHA Task Force on Practice Guidelines

1. Introduction

1.1. Organization of Committee and Evidence Review

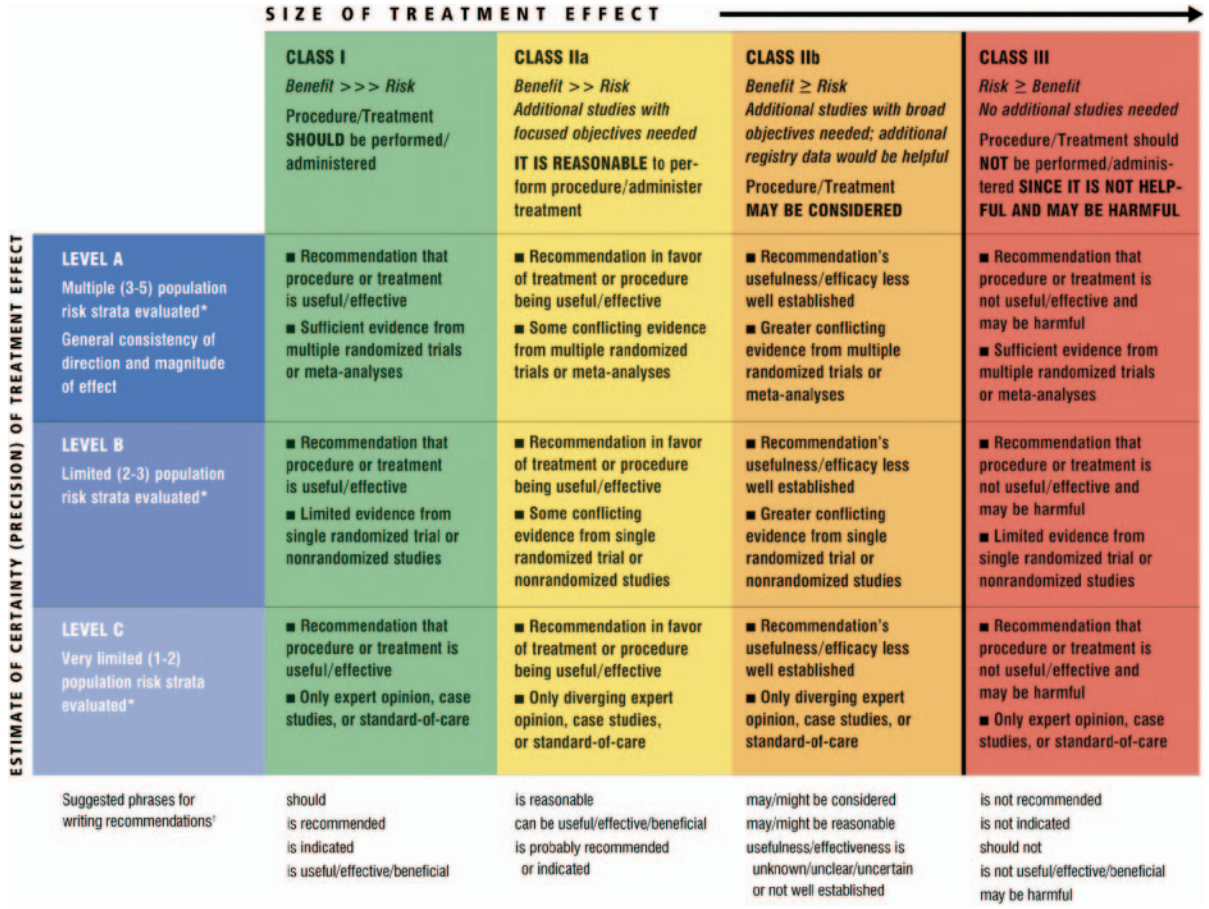
The ACC/AHA Task Force on Practice Guidelines was formed to make recommendations regarding the diagnosis and treatment of patients with known or suspected cardiovascular disease (CVD). Coronary artery disease (CAD) is the leading cause of death in the United States. Unstable angina (UA) and the closely related condition of non–ST-segment elevation myocardial infarction (NSTEMI) are very common manifestations of this disease.

The committee members reviewed and compiled published reports through a series of computerized literature searches of the English-language literature since 2002 and a final manual search of selected articles. Details of the specific searches conducted for particular sections are provided when appropriate. Detailed evidence tables were developed whenever necessary with the specific criteria outlined in the individual sections. The recommendations made were based primarily on these published data. The weight of the evidence was ranked highest (A) to lowest (C). The final recommendations for indications for a diagnostic procedure, a particular therapy, or an intervention in patients with UA/NSTEMI summarize both clinical evidence and expert opinion.

Classification of Recommendations

The schema for classification of recommendations and level of evidence is summarized in Table 1, which also illustrates

Table 1. Applying Classification of Recommendations and Level of Evidence†



ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT →			
	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	**CLASS IIa** *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	**CLASS IIb** *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	**CLASS III** *Risk ≥ Benefit* *No additional studies needed* Procedure/Treatment should **NOT** be performed/administered **SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL**
LEVEL A Multiple (3-5) population risk strata evaluated* General consistency of direction and magnitude of effect	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited (2-3) population risk strata evaluated*	■ Recommendation that procedure or treatment is useful/effective ■ Limited evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Limited evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited (1-2) population risk strata evaluated*	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard-of-care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard-of-care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard-of-care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard-of-care
Suggested phrases for writing recommendations‡	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective. †In 2003, the ACC/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All guideline recommendations have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers' comprehension of the guidelines and will allow queries at the individual recommendation level.

how the grading system provides an estimate of the size of the treatment effect and an estimate of the certainty of the treatment effect.

A complete list of the thousands of publications on various aspects of this subject is beyond the scope of these guidelines; only selected references are included. The Committee consisted of acknowledged experts in general internal medicine representing the American College of Physicians (ACP), family medicine from the American Academy of Family Physicians (AAFP), emergency medicine from the American College of Emergency Physicians (ACEP), thoracic surgery from the Society of Thoracic Surgeons (STS), interventional cardiology from the Society for Cardiovascular Angiography and Interventions (SCAI), and general and critical care cardiology, as well as individuals with recognized expertise in more specialized areas, including noninvasive testing, preventive cardiology, coronary intervention, and cardiovascular surgery. Both the academic and private practice sectors were represented. This document was reviewed by 2 outside reviewers nominated by each of the ACC and AHA and by 49 peer reviewers. These guidelines will be considered current unless the Task Force revises them or withdraws them from distribution.

These guidelines overlap several previously published ACC/AHA practice guidelines, including the ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (1), the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention (2), the AHA/ACC Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update (3), and the ACC/AHA 2002 Guideline Update for the Management of Patients With Chronic Stable Angina (4).

1.2. Purpose of These Guidelines

These guidelines address the diagnosis and management of patients with UA and the closely related condition of NSTEMI. These life-threatening disorders are a major cause of emergency medical care and hospitalization in the United States. In 2004, the National Center for Health Statistics reported 1,565,000 hospitalizations for primary or secondary diagnosis of an acute coronary syndrome (ACS), 669,000 for UA and 896,000 for myocardial infarction (MI) (5). The average age of a person having a first heart attack is 65.8 years for men and 70.4 years for women, and 43% of ACS patients of all ages are women. In 2003, there were 4,497,000 visits to US emergency departments (EDs) for primary diagnosis of CVD (5). The prevalence of this presentation of CVD ensures that many health care providers who are not cardiovascular specialists will encounter patients with UA/NSTEMI in the course of the treatment of other diseases, especially in outpatient and ED settings. These guidelines are intended to assist both cardiovascular specialists and nonspecialists in the proper evaluation and management of patients with an acute onset of symptoms suggestive of these conditions. These clinical practice guidelines also provide recommendations and supporting evidence for the continued management of patients with these conditions in both inpatient and outpatient settings. The diagnostic and therapeutic strategies that are recommended are supported by the best available evidence and expert opinion. The application of these principles with carefully reasoned clinical judgment reduces but does not eliminate the risk of cardiac damage and death in patients who present with symptoms suggestive of UA/NSTEMI.

1.3. Overview of the Acute Coronary Syndromes

1.3.1. Definition of Terms

Unstable angina/NSTEMI constitutes a clinical syndrome subset of the ACS that is usually, but not always, caused by atherosclerotic CAD and is associated with an increased risk of cardiac death and subsequent MI. In the spectrum of ACS, UA/NSTEMI is defined by electrocardiographic (ECG) ST-segment depression or prominent T-wave inversion and/or positive biomarkers of necrosis (e.g., troponin) in the absence of ST-segment elevation and in an appropriate clinical setting (chest discomfort or anginal equivalent) (Table 2, Fig. 1). The results of angiographic

Table 2. Guidelines for the Identification of ACS Patients by ED Registration Clerks or Triage Nurses

Registration/clerical staff

Patients with the following chief complaints require immediate assessment by the triage nurse and should be referred for further evaluation:

- Chest pain, pressure, tightness, or heaviness; pain that radiates to neck, jaw, shoulders, back, or 1 or both arms
- Indigestion or "heartburn"; nausea and/or vomiting associated with chest discomfort
- Persistent shortness of breath
- Weakness, dizziness, lightheadedness, loss of consciousness

Triage nurse

Patients with the following symptoms and signs require immediate assessment by the triage nurse for the initiation of the ACS protocol:

- Chest pain or severe epigastric pain, nontraumatic in origin, with components typical of myocardial ischemia or MI:
  - Central/substernal compression or crushing chest pain
  - Pressure, tightness, heaviness, cramping, burning, aching sensation
  - Unexplained indigestion, belching, epigastric pain
  - Radiating pain in neck, jaw, shoulders, back, or 1 or both arms
- **Associated dyspnea**
- **Associated nausea and/or vomiting**
- **Associated diaphoresis**

If these symptoms are present, obtain stat ECG.

Medical history

The triage nurse should take a brief, targeted, initial history with an assessment of current or past history of:

- CABG, PCI, CAD, angina on effort, or MI
- NTG use to relieve chest discomfort
- Risk factors, including smoking, hyperlipidemia, hypertension, diabetes mellitus, family history, and cocaine or methamphetamine use
- Regular and recent medication use

The brief history must not delay entry into the ACS protocol.

Special considerations

Women may present more frequently than men with atypical chest pain and symptoms.

Diabetic patients may have atypical presentations due to autonomic dysfunction.

Elderly patients may have atypical symptoms such as generalized weakness, stroke, syncope, or a change in mental status.

Adapted from National Heart Attack Alert Program. Emergency Department: rapid identification and treatment of patients with acute myocardial infarction. Bethesda, MD: US Department of Health and Human Services. US Public Health Service. National Institutes of Health. National Heart, Lung and Blood Institute, September 1993. NIH Publication No. 93-3278 (6).

ACS = acute coronary syndrome; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; ECG = electrocardiogram; ED = emergency department; MI = myocardial infarction; NTG = nitroglycerin; PCI = percutaneous coronary intervention.

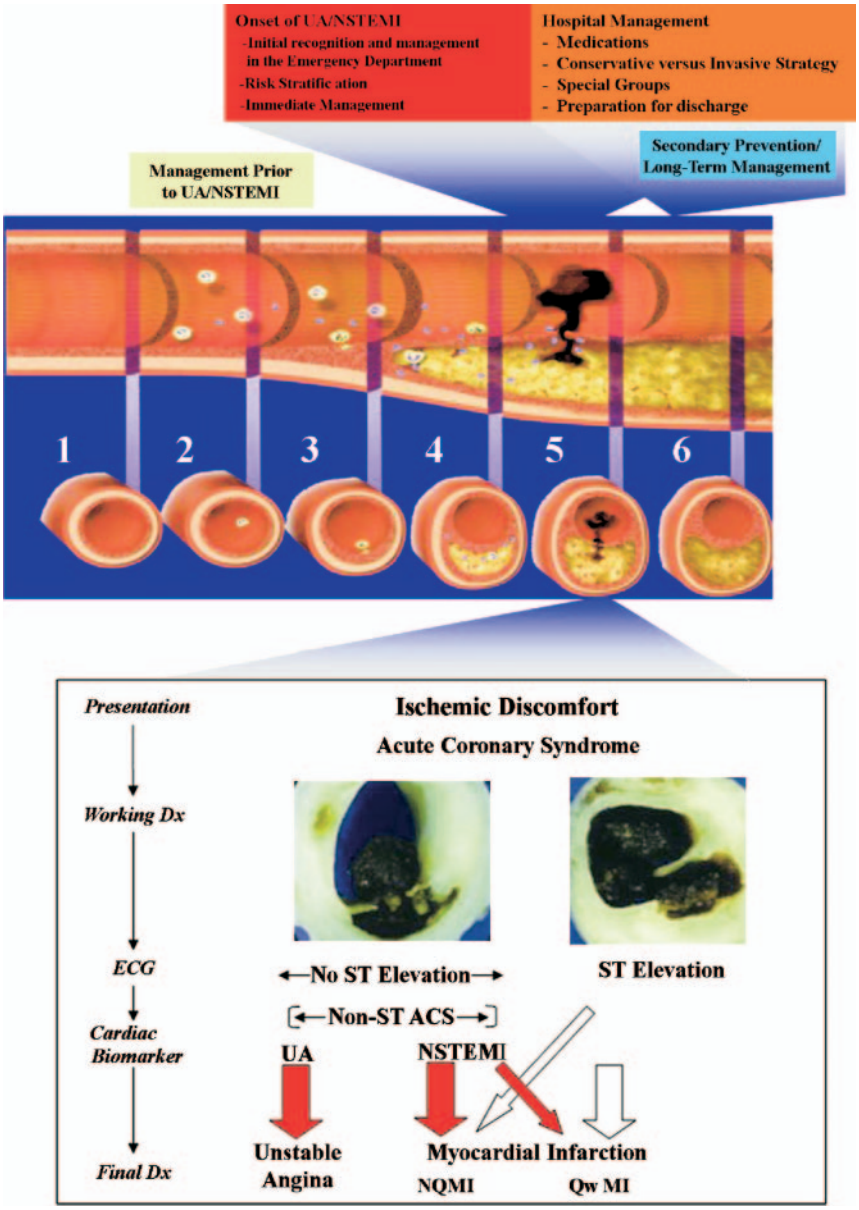


Figure 1. Acute Coronary Syndromes

The top half of the figure illustrates the chronology of the interface between the patient and the clinician through the progression of plaque formation, onset, and complications of UA/NSTEMI, along with relevant management considerations at each stage. The longitudinal section of an artery depicts the "timeline" of atherogenesis from (1) a normal artery to (2) lesion initiation and accumulation of extracellular lipid in the intima, to (3) the evolution to the fibrofatty stage, to (4) lesion progression with procoagulant expression and weakening of the fibrous cap. An acute coronary syndrome (ACS) develops when the vulnerable or high-risk plaque undergoes disruption of the fibrous cap (5); disruption of the plaque is the stimulus for thrombogenesis. Thrombus resorption may be followed by collagen accumulation and smooth muscle cell growth (6). After disruption of a vulnerable or high-risk plaque, patients experience ischemic discomfort that results from a reduction of flow through the affected epicardial coronary artery. The flow reduction may be caused by a completely occlusive thrombus (bottom half, right side) or subtotally occlusive thrombus (bottom half, left side). Patients with ischemic discomfort may present with or without ST-segment elevation on the ECG. Among patients with ST-segment elevation, most (thick white arrow in bottom panel) ultimately develop a Q-wave MI (QwMI), although a few (thin white arrow) develop a non–Q-wave MI (NQMI). Patients who present without ST-segment elevation are suffering from either unstable angina (UA) or a non–ST-segment elevation MI (NSTEMI) (thick red arrows), a distinction that is ultimately made on the basis of the presence or absence of a serum cardiac marker such as CK-MB or a cardiac troponin detected in the blood. Most patients presenting with NSTEMI ultimately develop a NQMI on the ECG; a few may develop a QwMI. The spectrum of clinical presentations ranging from UA through NSTEMI and STEMI is referred to as the acute coronary syndromes. This UA/NSTEMI guideline, as diagrammed in the upper panel, includes sections on initial management before UA/NSTEMI, at the onset of UA/NSTEMI, and during the hospital phase. Secondary prevention and plans for long-term management begin early during the hospital phase of treatment. *Positive serum cardiac marker. Modified with permission from Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. Circulation 2001;104:365 (7); © 2001 Lippincott, Williams & Wilkins; The Lancet, 358, Hamm CW, Bertrand M, Braunwald E. Acute coronary syndrome without ST elevation: implementation of new guidelines, 1553–8. Copyright 2001, with permission from Elsevier (8); and Davies MJ. The pathophysiology of acute coronary syndromes. Heart 2000;83:361–6 (9). © 2000 Lippincott, Williams & Wilkins. CK-MB = MB fraction of creatine kinase; Dx = diagnosis; ECG = electrocardiogram.

and angioscopic studies suggest that UA/NSTEMI often results from the disruption or erosion of an atherosclerotic plaque and a subsequent cascade of pathological processes that decrease coronary blood flow. Most patients who die during UA/NSTEMI do so because of sudden death or the development (or recurrence) of acute MI. The efficient diagnosis and optimal management of these patients must derive from information readily available at the time of the initial clinical presentation. The clinical presentation of patients with a life-threatening ACS often overlaps that of patients subsequently found not to have CAD. Moreover, some forms of MI cannot always be differentiated from UA at the time of initial presentation.

"Acute coronary syndrome" has evolved as a useful operational term to refer to any constellation of clinical symptoms that are compatible with acute myocardial ischemia (Fig. 1). It encompasses MI (ST-segment elevation and depression, Q wave and non-Q wave) and UA. These guidelines focus on 2 components of this syndrome: UA and NSTEMI. In practice, the term "possible ACS" is often assigned first by ancillary personnel, such as emergency medical technicians and triage nurses, early in the evaluation process. A guideline of the National Heart Attack Alert Program (6) summarizes the clinical information needed to make the diagnosis of possible ACS at the earliest phase of clinical evaluation (Table 2). The implication of this early diagnosis for clinical management is that a patient who is considered to have an ACS should be placed in an environment with continuous ECG monitoring and defibrillation capability, where a 12-lead ECG can be obtained expeditiously and definitively interpreted, ideally within 10 min of arrival in the ED. The most urgent priority of early evaluation is to identify patients with ST-elevation MI (STEMI) who should be considered for immediate reperfusion therapy and to recognize other potentially catastrophic causes of patient symptoms, such as aortic dissection.

Patients diagnosed as having STEMI are excluded from management according to these guidelines and should be managed as indicated according to the ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (1,10). Similarly, management of electrocardiographic true posterior MI, which can masquerade as NSTEMI, is covered in the STEMI guidelines (1). The management of patients who experience periprocedural myocardial damage, as reflected in the release of biomarkers of necrosis, such as the MB isoenzyme of creatine kinase (CK-MB) or troponin, also is not considered here.

Patients with MI and with definite ischemic ECG changes for whom acute reperfusion therapy is not suitable should be diagnosed and managed as patients with UA. The residual group of patients with an initial diagnosis of ACS will include many patients who will ultimately be proven to have a noncardiac cause for the initial clinical presentation that was suggestive of ACS. Therefore, at the conclusion of the initial evaluation, which is frequently performed in the ED but sometimes occurs during the initial hours of inpatient hospitalization, each patient should have a provisional diagnosis of 1) ACS (Fig. 1), which in turn is classified as a) STEMI, a condition for which immediate reperfusion therapy (fibrinolysis or percutaneous coronary intervention [PCI]) should be considered, b) NSTEMI, or c) UA (definite, probable, or possible); 2) a non-ACS cardiovascular condition (e.g., acute pericarditis); 3) a noncardiac condition with another specific disease (e.g., chest pain secondary to esophageal spasm); or 4) a noncardiac condition that is undefined. In addition, the initial evaluation should be used to determine risk and to treat life-threatening events.

In these guidelines, UA and NSTEMI are considered to be closely related conditions whose pathogenesis and clinical presentations are similar but of differing severity; that is, they differ primarily in whether the ischemia is severe enough to cause sufficient myocardial damage to release detectable quantities of a marker of myocardial injury, most commonly troponin I (TnI), troponin T (TnT), or CK-MB. Once it has been established that no biomarker of myocardial necrosis has been released (based on 2 or more samples collected at least 6 h apart, with a reference limit of the 99th percentile of the normal population) (11), the patient with ACS may be considered to have experienced UA, whereas the diagnosis of NSTEMI is established if a biomarker has been released. Markers of myocardial injury can be detected in the bloodstream with a delay of up to several hours after the onset of ischemic chest pain, which then allows the differentiation between UA (i.e., no biomarkers in circulation; usually transient, if any, ECG changes of ischemia) and NSTEMI (i.e., elevated biomarkers). Thus, at the time of presentation, patients with UA and NSTEMI can be indistinguishable and therefore are considered together in these guidelines.

1.3.2. Pathogenesis of UA/NSTEMI

These conditions are characterized by an imbalance between myocardial oxygen supply and demand. They are not a specific disease, such as pneumococcal pneumonia, but rather a syndrome, analogous to hypertension. A relatively few nonexclusive causes are recognized (12) (Table 3).

The most common mechanisms involve an imbalance that is caused primarily by a reduction in oxygen supply to the myocardium, whereas with the fifth mechanism noted below, the imbalance is principally due to increased myocardial oxygen requirements, usually in the presence of a fixed, restricted oxygen supply:

- The most common cause of UA/NSTEMI is reduced myocardial perfusion that results from coronary artery narrowing caused by a thrombus that developed on a disrupted atherosclerotic plaque and is usually nonocclusive. Microembolization of platelet aggregates and components of the disrupted plaque are believed to be responsible for the release of myocardial markers in many of these patients. An occlusive thrombus/plaque also can

Table 3. Causes of UA/NSTEMI*

Thrombus or thromboembolism, usually arising on disrupted or eroded plaque
• Occlusive thrombus, usually with collateral vessels†
• Subtotally occlusive thrombus on pre-existing plaque
• Distal microvascular thromboembolism from plaque-associated thrombus
Thromboembolism from plaque erosion
• Non–plaque-associated coronary thromboembolism
Dynamic obstruction (coronary spasm‡ or vasoconstriction) of epicardial and/or microvascular vessels
Progressive mechanical obstruction to coronary flow
Coronary arterial inflammation
Secondary UA
Coronary artery dissection§

*These causes are not mutually exclusive; some patients have 2 or more causes. †DeWood MA, Stifter WF, Simpson CS, et al. Coronary arteriographic findings soon after non–Q-wave myocardial infarction. N Engl J Med 1986;315:417–23 (13). ‡May occur on top of an atherosclerotic plaque, producing missed-etiology angina or UA/NSTEMI. §Rare. Modified with permission from Braunwald E. Unstable angina: an etiologic approach to management. Circulation 1998;98:2219–22 (12).

UA = unstable angina; UA/NSTEMI = unstable angina/non–ST-elevation myocardial infarction.

cause this syndrome in the presence of an extensive collateral blood supply.

- The most common underlying molecular and cellular pathophysiology of disrupted atherosclerotic plaque is arterial inflammation, caused by noninfectious (e.g., oxidized lipids) and, possibly, infectious stimuli, which can lead to plaque expansion and destabilization, rupture or erosion, and thrombogenesis. Activated macrophages and T lymphocytes located at the shoulder of a plaque increase the expression of enzymes such as metalloproteinases that cause thinning and disruption of the plaque, which in turn can lead to UA/NSTEMI.
- A less common cause is dynamic obstruction, which may be triggered by intense focal spasm of a segment of an epicardial coronary artery (Prinzmetal's angina) (see Section 6.7). This local spasm is caused by hypercontractility of vascular smooth muscle and/or by endothelial dysfunction. Large-vessel spasm can occur on top of obstructive or destabilized plaque, resulting in angina of "mixed" origin or UA/NSTEMI. Dynamic coronary obstruction can also be caused by diffuse microvascular dysfunction; for example, due to endothelial dysfunction or the abnormal constriction of small intramural resistance vessels. Coronary spasm also is the presumed mechanism underlying cocaine-induced UA/NSTEMI.
- A third cause of UA/NSTEMI is severe narrowing without spasm or thrombus. This occurs in some patients with progressive atherosclerosis or with restenosis after a PCI.
- A fourth cause of UA/NSTEMI is coronary artery dissection (e.g., as a cause of ACS in peripartal women).
- The fifth mechanism is secondary UA, in which the precipitating condition is extrinsic to the coronary arterial bed. Patients with secondary UA usually, but not always, have underlying coronary atherosclerotic narrowing that limits myocardial perfusion, and they often have chronic stable angina. Secondary UA is precipitated by conditions that 1) increase myocardial oxygen requirements, such as fever, tachycardia, or thyrotoxicosis; 2) reduce coronary blood flow, such as hypotension; or 3) reduce myocardial oxygen delivery, such as anemia or hypoxemia.

These causes of UA/NSTEMI are not mutually exclusive.

Table 4. Three Principal Presentations of UA

Class	Presentation
Rest angina*	Angina occurring at rest and prolonged, usually greater than 20 min
New-onset angina	New-onset angina of at least CCS class III severity
Increasing angina	Previously diagnosed angina that has become distinctly more frequent, longer in duration, or lower in threshold (i.e., increased by 1 or more CCS class to at least CCS class III severity)

*Patients with non–ST-elevated myocardial infarction usually present with angina at rest. Adapted with permission from Braunwald E. Unstable angina: a classification. Circulation 1989;80:410–4 (14).

CCS = Canadian Cardiovascular Society classification; UA = unstable angina.

1.3.3. Presentations of UA and NSTEMI

There are 3 principal presentations of UA: 1) rest angina (angina commencing when the patient is at rest), 2) new-onset (less than 2 months) severe angina, and 3) increasing angina (increasing in intensity, duration, and/or frequency) (Table 4) (14). Criteria for the diagnosis of UA are based on the duration and intensity of angina as graded according to the Canadian Cardiovascular Society classification (Table 5) (15). Non–ST-elevation MI generally presents as prolonged, more intense rest angina or angina equivalent.

1.4. Management Before UA/NSTEMI and Onset of UA/NSTEMI

The ACS spectrum (UA/MI) has a variable but potentially serious prognosis. The major risk factors for development of coronary heart disease (CHD) and UA/NSTEMI are well established. Clinical trials have demonstrated that modifi-

Table 5. Grading of Angina Pectoris According to CCS Classification

Class	Description of Stage
I	"Ordinary physical activity does not cause . . . angina," such as walking or climbing stairs. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.
II	"Slight limitation of ordinary activity." Angina occurs on walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals; in cold, in wind, or under emotional stress; or only during the few hours after awakening. Angina occurs on walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and under normal conditions.
III	"Marked limitations of ordinary physical activity." Angina occurs on walking 1 to 2 blocks on the level and climbing 1 flight of stairs under normal conditions and at a normal pace.
IV	"Inability to carry on any physical activity without discomfort—anginal symptoms may be present at rest."

Adapted with permission from Campeau L. Grading of angina pectoris (letter). Circulation 1976;54:522–3 (15).

CCS = Canadian Cardiovascular Society.

cation of those risk factors can prevent the development of CHD (primary prevention) or reduce the risk of experiencing UA/NSTEMI in patients who have CHD (secondary prevention). All practitioners should emphasize prevention and refer patients to primary care providers for appropriate long-term preventive care. In addition to internists and family physicians, cardiologists have an important leadership role in primary (and secondary) prevention efforts.

1.4.1. Identification of Patients at Risk of UA/NSTEMI

CLASS I

1. **Primary care providers should evaluate the presence and status of control of major risk factors for CHD for all patients at regular intervals (approximately every 3 to 5 years). *(Level of Evidence: C)***
2. **Ten-year risk (National Cholesterol Education Program [NCEP] global risk) of developing symptomatic CHD should be calculated for all patients who have 2 or more major risk factors to assess the need for primary prevention strategies (16,17). *(Level of Evidence: B)***
3. **Patients with established CHD should be identified for secondary prevention efforts, and patients with a CHD risk equivalent (e.g., atherosclerosis in other vascular beds, diabetes mellitus, chronic kidney disease, or 10-year risk greater than 20% as calculated by Framingham equations) should receive equally intensive risk factor intervention as those with clinically apparent CHD. *(Level of Evidence: A)***

Major risk factors for developing CHD (i.e., smoking, family history, adverse lipid profiles, diabetes mellitus, and elevated blood pressure) have been established from large, long-term epidemiological studies (18,19). These risk factors are predictive for most populations in the United States. Primary and secondary prevention interventions aimed at these risk factors are effective when used properly. They can also be costly in terms of primary care provider time, diversion of attention from other competing and important health care needs, and expense, and they may not be effective unless targeted at higher-risk patients (20). It is therefore important for primary care providers to make the identification of patients at risk, who are most likely to benefit from primary prevention, a routine part of everyone's health care. The Third Report of the NCEP provides guidance on identifying such patients (18). Furthermore, the Writing Committee supports public health efforts to reach all adults at risk, not just those under the care of a primary care physician.

Patients with 2 or more risk factors who are at increased 10-year and lifetime risk will have the greatest benefit from primary prevention, but any individual with a single elevated risk factor is a candidate for primary prevention (19). Waiting until the patient develops multiple risk factors and increased 10-year risk contributes to the high prevalence of CHD in the United States (18,21). Such patients should have their risk specifically calculated by any of the several valid prognostic tools available in print (18,22), on the Internet (23), or for use on a personal computer or personal digital assistant (PDA) (18). Patients' specific risk levels determine the absolute risk reductions they can obtain from preventive interventions and guide selection and prioritization of those interventions. For example, target levels for lipid lowering and for antihypertensive therapy vary by patients' baseline risk. A specific risk number can also serve as a powerful educational intervention to motivate lifestyle changes (24).

The detection of subclinical atherosclerosis by noninvasive imaging represents a new, evolving approach for refining individual risk in asymptomatic individuals beyond traditional risk factor assessment alone. A recent AHA scientific statement indicates that it may be reasonable to measure atherosclerosis burden using electron-beam or multidetector computed tomography (CT) in clinically selected intermediate-CAD-risk individuals (e.g., those with a 10% to 20% Framingham 10-year risk estimate) to refine clinical risk prediction and to select patients for aggressive target values for lipid-lowering therapies (Class IIb, Level of Evidence: B) (25).

1.4.2. Interventions to Reduce Risk of UA/NSTEMI

The benefits of prevention of UA/NSTEMI in patients with CHD are well documented and of large magnitude (3,21,26–28). Patients with established CHD should be identified for secondary prevention efforts, and patients with a CHD risk equivalent should receive equally intensive risk factor intervention for high-risk primary prevention regardless of sex (29). Patients with diabetes mellitus and peripheral vascular disease have baseline risks of UA/NSTEMI similar to patients with known CHD, as do patients with multiple risk factors that predict a calculated risk of greater than 20% over 10 years as estimated by the Framingham equations (18). Such patients should be considered to have the risk equivalents of CHD, and they can be expected to have an absolute benefit similar to those with established CHD.

All patients who use tobacco should be encouraged to quit and should be provided with help in quitting at every opportunity (30). Recommendations by a clinician to avoid tobacco can have a meaningful impact on the rate of cessation of tobacco use. The most effective strategies for encouraging quitting are those that identify the patient's level or stage of readiness and provide information, support, and, if necessary, pharmacotherapy targeted at the individual's readiness and specific needs (26,31). Pharmacotherapy may include nicotine replacement or withdrawal-relieving medication such as bupropion. Varenicline, a nicotine acetylcholine receptor partial antagonist, is a newly approved nonnicotine replacement therapy for tobacco avoidance (32–35). Many patients require several attempts before they succeed in quitting permanently (36,37). Additional discussion in this area can be found in other contemporary documents (e.g., the ACC/AHA 2002 Guideline Update for the Management of Patients With Chronic Stable Angina [4]).

All patients should be instructed in and encouraged to maintain appropriate low-saturated-fat, low-trans-fat, and

low-cholesterol diets high in soluble (viscous) fiber and rich in vegetables, fruits, and whole grains. All patients also should be encouraged to be involved with a regular aerobic exercise program, including 30 to 60 min of moderate-intensity physical activity (such as brisk walking) on most and preferably all days of the week (3,38). For those who need to weigh less, an appropriate balance of increased physical activity (i.e., 60 to 90 min daily), caloric restriction, and formal behavioral programs is encouraged to achieve and maintain a body mass index between 18.5 and 24.9 kg/m^2 and a waist circumference of less than or equal to 35 inches in women and less than or equal to 40 inches in men. For those who need lipid lowering beyond lifestyle measures, the statin drugs have the best outcome evidence supporting their use and should be the mainstay of pharmacological intervention (21). The appropriate levels for lipid management are dependent on baseline risk; the reader is referred to the NCEP report (http://www.nhlbi.nih.gov/guidelines/cholesterol/index.htm) for details (17,18,39–41).

Primary prevention patients with high blood pressure should be treated according to the recommendations of the Seventh Joint National Committee on High Blood Pressure (JNC 7) (42,43). Specific treatment recommendations are based on the level of hypertension and the patient's other risk factors. A diet low in salt and rich in vegetables, fruits, and low-fat dairy products should be encouraged for all hypertensive patients, as should a regular aerobic exercise program (44–47). Most patients will require more than 1 medication to achieve blood pressure control, and pharmacotherapy should begin with known outcome-improving medications (primarily thiazide diuretics as first choice, with the addition of beta blockers, angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers, and/or long-acting calcium channel blockers) (42,48). Systolic hypertension is a powerful predictor of adverse outcome, particularly among the elderly, and it should be treated even if diastolic pressures are normal (49).

Detection of hyperglycemic risk (e.g., metabolic syndrome) and diabetes mellitus should be pursued as part of risk assessment. Lifestyle changes and pharmacotherapy are indicated in individuals with diabetes mellitus to achieve a glycosylated hemoglobin [HbA1c] level less than 7% but to avoid hypoglycemia (3,50,51).

Aspirin prophylaxis can uncommonly result in hemorrhagic complications and should only be used in primary prevention when the level of risk justifies it. Patients whose 10-year risk of CHD is 10% or more are most likely to benefit, and 75 to 162 mg of aspirin (ASA) per day as primary prophylaxis should be discussed with such patients (29,38,52–55).

1.5. Onset of UA/NSTEMI

1.5.1. Recognition of Symptoms by Patient

Early recognition of symptoms of UA/NSTEMI by the patient or someone with the patient is the first step that must occur before evaluation and life-saving treatment can be obtained. Although many laypersons are generally aware that chest pain is a presenting symptom of UA/NSTEMI, they are unaware of the other common symptoms, such as arm pain, lower jaw pain, shortness of breath (56), and diaphoresis (57) or anginal equivalents, such as dyspnea or extreme fatigue (56,58). The average patient with NSTEMI or prolonged rest UA (e.g., longer than 20 min) does not seek medical care for approximately 2 h after symptom onset, and this pattern appears unchanged over the last decade (58–60). A baseline analysis from the Rapid Early Action for Coronary Treatment (REACT) research program demonstrated longer delay times among non-Hispanic blacks, older patients, and Medicaid-only recipients and shorter delay times among Medicare recipients (compared with privately insured patients) and patients who came to the hospital by ambulance (58). In the majority of studies examined to date, women in both univariate- and multivariate-adjusted analyses (in which age and other potentially confounding variables have been controlled) exhibit more prolonged delay patterns than men (61).

A number of studies have provided insight into why patients delay in seeking early care for heart symptoms (62). Focus groups conducted for the REACT research program (63,64) revealed that patients commonly hold a preexisting expectation that a heart attack would present dramatically with severe, crushing chest pain, such that there would be no doubt that one was occurring. This was in contrast to their actual reported symptom experience of a gradual onset of discomfort involving midsternal chest pressure or tightness, with other associated symptoms often increasing in intensity. The ambiguity of these symptoms, due to this disconnect between prior expectations and actual experience, resulted in uncertainty about the origin of symptoms and thus a "wait-and-see" posture by patients and those around them (62). Other reported reasons for delay were that patients thought the symptoms were self-limited and would go away or were not serious (65–67); that they attributed symptoms to other preexisting chronic conditions, especially among older adults with multiple chronic conditions (e.g., arthritis), or sometimes to a common illness such as influenza; that they were afraid of being embarrassed if symptoms turned out to be a "false alarm"; that they were reluctant to trouble others (e.g., health care providers, Emergency Medical Services [EMS]) unless they were "really sick" (65–67); that they held stereotypes of who is at risk for a heart attack; and that they lacked awareness of the importance of rapid action, knowledge of reperfusion treatment, or knowledge of the benefits of calling EMS/9-1-1 to ensure earlier treatment (62). Notably, women did not perceive themselves to be at risk (69).

1.5.2. Silent and Unrecognized Events

Patients experiencing UA/NSTEMI do not always present with chest discomfort (70). The Framingham Study was the

first to show that as many as half of all MIs may be clinically silent and unrecognized by the patient (71). Canto et al. (72) found that one third of the 434,877 patients with confirmed MI in the National Registry of Myocardial Infarction presented to the hospital with symptoms other than chest discomfort. Compared with MI patients with chest discomfort, MI patients without chest discomfort were more likely to be older, to be women, to have diabetes, and/or to have prior heart failure [HF]. Myocardial infarction patients without chest discomfort delayed longer before they went to the hospital (mean 7.9 vs. 5.3 h) and were less likely to be diagnosed as having an MI when admitted (22.2% vs. 50.3%). They also were less likely to receive fibrinolysis or primary PCI, ASA, beta blockers, or heparin. Silent MI patients were 2.2 times more likely to die during the hospitalization (in-hospital mortality rate 23.3% vs. 9.3%). Unexplained dyspnea, even without angina, is a particularly worrisome symptom, with more than twice the risk of death than for typical angina in patients undergoing cardiovascular evaluation (56). Recently, the prognostic significance of dyspnea has been emphasized in patients undergoing cardiac evaluation. Self-reported dyspnea alone among 17,991 patients undergoing stress perfusion testing was an independent predictor of cardiac and total mortality and increased the risk of sudden cardiac death 4-fold even in those with no prior history of CAD (56).

Health care providers should maintain a high index of suspicion for UA/NSTEMI when evaluating women, patients with diabetes mellitus, older patients, those with unexplained dyspnea (56), and those with a history of HF or stroke, as well as those patients who complain of chest discomfort but who have a permanent pacemaker that may confound recognition of UA/NSTEMI on their 12-lead ECG (73).

2. Initial Evaluation and Management

2.1. Clinical Assessment

Because symptoms are similar and the differentiation of UA/NSTEMI and STEMI requires medical evaluation, we will refer to prediagnostic clinical presentation as ACS, defined as UA or MI (NSTEMI or STEMI) (Fig. 2).

RECOMMENDATIONS

CLASS I

1. **Patients with symptoms that may represent ACS (Table 2) should not be evaluated solely over the telephone but should be referred to a facility that allows evaluation by a physician and the recording of**

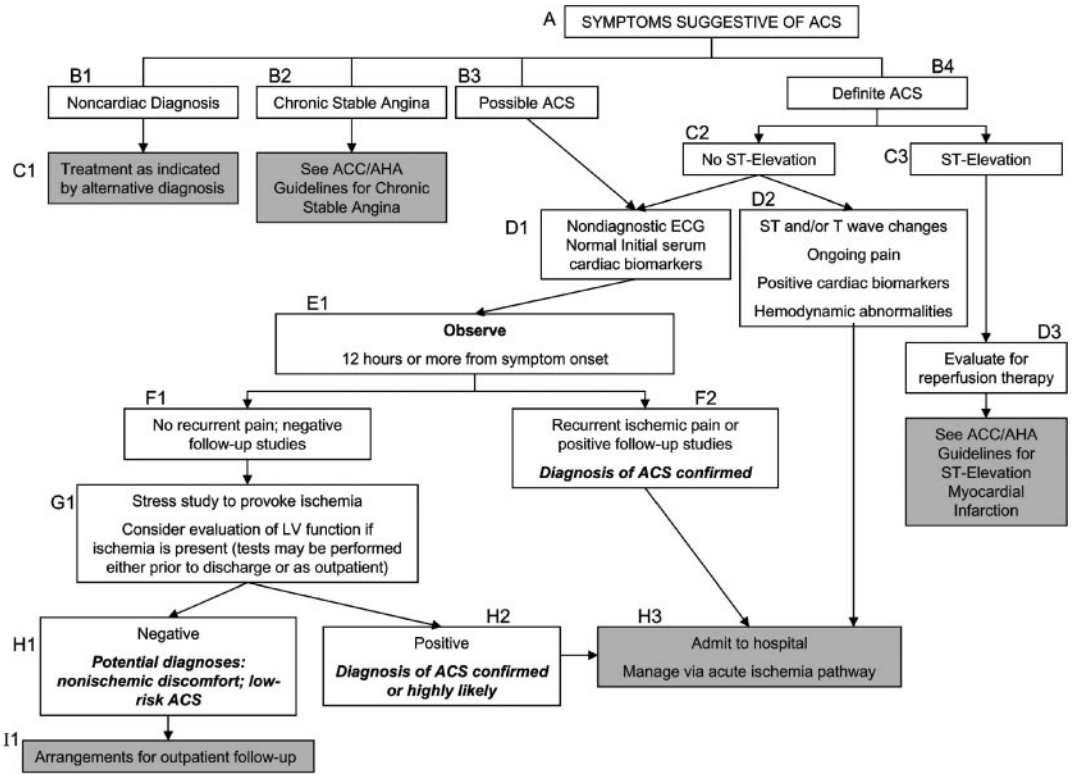


Figure 2. Algorithm for Evaluation and Management of Patients Suspected of Having ACS

To facilitate interpretation of this algorithm and a more detailed discussion in the text, each box is assigned a letter code that reflects its level in the algorithm and a number that is allocated from left to right across the diagram on a given level. ACC/AHA = American College of Cardiology/American Heart Association; ACS = acute coronary syndrome; ECG = electrocardiogram; LV = left ventricular.

a 12-lead ECG and biomarker determination (e.g., an ED or other acute care facility). *(Level of Evidence: C)*

2. Patients with symptoms of ACS (chest discomfort with or without radiation to the arm[s], back, neck, jaw or epigastrium; shortness of breath; weakness; diaphoresis; nausea; lightheadedness) should be instructed to call 9-1-1 and should be transported to the hospital by ambulance rather than by friends or relatives. *(Level of Evidence: B)*
3. Health care providers should actively address the following issues regarding ACS with patients with or at risk for CHD and their families or other responsible caregivers:
   a. The patient's heart attack risk; *(Level of Evidence: C)*
   b. How to recognize symptoms of ACS; *(Level of Evidence: C)*
   c. The advisability of calling 9-1-1 if symptoms are unimproved or worsening after 5 min, despite feelings of uncertainty about the symptoms and fear of potential embarrassment; *(Level of Evidence: C)*
   d. A plan for appropriate recognition and response to a potential acute cardiac event, including the phone number to access EMS, generally 9-1-1 (74). *(Level of Evidence: C)*
4. Prehospital EMS providers should administer 162 to 325 mg of ASA (chewed) to chest pain patients suspected of having ACS unless contraindicated or already taken by the patient. Although some trials have used enteric-coated ASA for initial dosing, more rapid buccal absorption occurs with non–enteric-coated formulations. *(Level of Evidence: C)*
5. Health care providers should instruct patients with suspected ACS for whom nitroglycerin [NTG] has been prescribed previously to take not more than 1 dose of NTG sublingually in response to chest discomfort/pain. If chest discomfort/pain is unimproved or is worsening 5 min after 1 NTG dose has been taken, it is recommended that the patient or family member/friend/caregiver call 9-1-1 immediately to access EMS before taking additional NTG. In patients with chronic stable angina, if symptoms are significantly improved by 1 dose of NTG, it is appropriate to instruct the patient or family member/friend/caregiver to repeat NTG every 5 min for a maximum of 3 doses and call 9-1-1 if symptoms have not resolved completely. *(Level of Evidence: C)*
6. Patients with a suspected ACS with chest discomfort or other ischemic symptoms at rest for greater than 20 min, hemodynamic instability, or recent syncope or presyncope should be referred immediately to an ED. Other patients with suspected ACS who are experiencing less severe symptoms and who have none of the above high-risk features, including those who respond to an NTG dose, may be seen initially in an ED or an outpatient facility able to provide an acute evaluation. *(Level of Evidence: C)*

CLASS IIa

1. It is reasonable for health care providers and 9-1-1 dispatchers to advise patients without a history of ASA allergy who have symptoms of ACS to chew ASA (162 to 325 mg) while awaiting arrival of prehospital EMS providers. Although some trials have used enteric-coated ASA for initial dosing, more rapid buccal absorption occurs with non–enteric-coated formulations. *(Level of Evidence: B)*
2. It is reasonable for health care providers and 9-1-1 dispatchers to advise patients who tolerate NTG to repeat NTG every 5 min for a maximum of 3 doses while awaiting ambulance arrival. *(Level of Evidence: C)*
3. It is reasonable that all prehospital EMS providers perform and evaluate 12-lead ECGs in the field (if available) on chest pain patients suspected of ACS to assist in triage decisions. Electrocardiographs with validated computer-generated interpretation algorithms are recommended for this purpose. *(Level of Evidence: B)*
4. If the 12-lead ECG shows evidence of acute injury or ischemia, it is reasonable that prehospital ACLS providers relay the ECG to a predetermined medical control facility and/or receiving hospital. *(Level of Evidence: B)*

Patients with suspected ACS must be evaluated rapidly. Decisions made on the basis of the initial evaluation have substantial clinical and economic consequences (75). The first triage decision is made by the patient, who must decide whether to access the health care system. Media campaigns such as "Act in Time," sponsored by the National Heart, Lung, and Blood Institute (NHLBI), provide patient education regarding this triage decision (www.nhlbi.nih.gov/actintime). The campaign urges both men and women who feel heart attack symptoms or observe the signs in others to wait no more than a few minutes, 5 min at most, before calling 9-1-1 (76,77). Campaign materials point out that patients can increase their chance of surviving a heart attack by learning the symptoms and filling out a survival plan. They also are advised to talk with their doctor about heart attacks and how to reduce their risk of having one. The patient materials include a free brochure about symptoms and recommended actions for survival, in English (78) and Spanish (79), as well as a free wallet card that can be filled in with emergency medical information (80). Materials geared directly to providers include a Patient Action Plan Tablet (81), which contains the heart attack warning symptoms and steps for developing a survival plan, individualized with the patient's name; a quick reference card for addressing common patient questions about seeking early treatment to survive a heart attack (82), including a PDA version (83); and a warning signs wall chart (84). These materials and others are available on the "Act in Time" Web page (www.nhlbi.nih.gov/health/public/heart/mi/core_bk.pdf) (77).

When the patient first makes contact with the medical care system, a critical decision must be made about where the evaluation will take place. The health care provider then must place the evaluation in the context of 2 critical questions: Are the symptoms a manifestation of an ACS? If so, what is the prognosis? The answers to these 2 questions lead logically to a series of decisions about where the patient will be best managed, what medications will be prescribed, and whether an angiographic evaluation will be required.

Given the large number of patients with symptoms compatible with ACS, the heterogeneity of the population, and a clustering of events shortly after the onset of symptoms, a strategy for the initial evaluation and management is essential. Health care providers may be informed about signs and symptoms of ACS over the telephone or in person by the patient or family members. The objectives of the initial evaluation are first to identify signs of immediate life-threatening instability and then to ensure that the patient is moved rapidly to the most appropriate environ-

ment for the level of care needed based on diagnostic criteria and an estimation of the underlying risk of specific negative outcomes.

Health practitioners frequently receive telephone calls from patients or family members/friends/caregivers who are concerned that their symptoms could reflect heart disease. Most such calls regarding chest discomfort of possible cardiac origin in patients without known CAD do not represent an emergency; rather, these patients usually seek reassurance that they do not have heart disease or that there is little risk due to their symptoms. Despite the frequent inclination to dismiss such symptoms over the telephone, health care providers, EMS dispatchers, and staff positioned to receive these calls should advise patients with possible accelerating angina or angina at rest that an evaluation cannot be performed solely via the telephone. This advice is essential because of the need for timely evaluation, including a physical examination, ECG, and appropriate blood tests to measure cardiac biomarkers.

Patients with known CAD—including those with chronic stable angina, recent MI, or prior intervention (i.e., coronary artery bypass graft surgery [CABG] or PCI)—who contact a physician or other appropriate member of the health care team because of worsening or recurrent symptoms should be instructed to proceed rapidly to an ED, preferably one equipped to perform prompt reperfusion therapy. When the discomfort is moderate to severe or sustained, they should be instructed to access the EMS system directly by calling 9-1-1. Patients who have been evaluated recently and who are calling for advice regarding modification of medications as part of an ongoing treatment plan represent exceptions.

Even in the most urgent subgroup of patients who present with acute-onset chest pain, there usually is adequate time for transport to an environment in which they can be evaluated and treated (85). In a large study of consecutive patients with chest pain suspected to be of cardiac origin who were transported to the ED via ambulance, one third had a final diagnosis of MI, one third had a final diagnosis of UA, and one third had a final diagnosis of a noncardiac cause; 1.5% of these patients developed cardiopulmonary arrest before arrival at the hospital or in the ED (86).

Every community should have a written protocol that guides EMS system personnel in determining where to take patients with suspected or confirmed ACS. Active involvement of local health care providers, particularly cardiologists and emergency physicians, is needed to formulate local EMS destination protocols for these patients. In general, patients with suspected ACS should be taken to the nearest appropriate hospital; however, patients with known STEMI and/or cardiogenic shock should be sent as directly as possible to hospitals with interventional and surgical capability (1).

The advent of highly effective, time-dependent treatment for ACS, coupled with the need to reduce health care costs, adds further incentive for clinicians to get the right answer quickly and to reduce unnecessary admissions and length of hospital stay. Investigators have tried various diagnostic tools, such as clinical decision algorithms, cardiac biomarkers, serial ECGs, echocardiography, myocardial perfusion imaging, and multidetector (e.g., 64-slice) coronary CT angiography (CCTA), in an attempt to avoid missing patients with MI or UA. The most successful strategies to emerge thus far are designed to identify MI patients and, when clinically appropriate, screen for UA and underlying CAD. Most strategies use a combination of cardiac biomarkers, short-term observation, diagnostic imaging, and provocative stress testing. An increasing number of high-quality centers now use structured protocols, checklists, or critical pathways to screen patients with suspected MI or UA (87–99). It does not appear to matter whether the institution designates itself a chest pain center; rather, it is the multifaceted, multidisciplinary, standardized, and structured approach to the problem that appears to provide clinical, cost-effective benefit (100,101). One randomized trial has confirmed the safety, efficacy, and cost-effectiveness of the structured decision-making approach compared with standard, unstructured care (102).

Regardless of the approach used, all patients presenting to the ED with chest discomfort or other symptoms suggestive of MI or UA should be considered high-priority triage cases and should be evaluated and treated on the basis of a predetermined, institution-specific chest pain protocol. The protocol should include several diagnostic possibilities (Fig. 2) (103). The patient should be placed on a cardiac monitor immediately, with emergency resuscitation equipment, including a defibrillator, nearby. An ECG also should be performed immediately and evaluated by an experienced emergency medicine physician, with a goal of within 10 min of ED arrival. If STEMI is present, the decision as to whether the patient will be treated with fibrinolytic therapy or primary PCI should be made within the next 10 min (1). For cases in which the initial diagnosis and treatment plan are unclear to the emergency medicine physician or are not covered directly by an institutionally agreed-upon protocol, immediate cardiology consultation is advisable.

Morbidity and mortality from ACS can be reduced significantly if patients and bystanders recognize symptoms early, activate the EMS system, and thereby shorten the time to definitive treatment. Patients with possible symptoms of MI should be transported to the hospital by ambulance rather than by friends or relatives, because there is a significant association between arrival at the ED by ambulance and early reperfusion therapy in STEMI patients (104–107). In addition, emergency medical technicians and paramedics can provide life-saving interventions (e.g., early cardiopulmonary resuscitation [CPR] and defibrillation) if the patient develops cardiac arrest. Approximately 1 in every 300 patients with chest pain transported to the ED by private vehicle goes into cardiac arrest en route (108).

Several studies have confirmed that patients with ACS frequently do not call 9-1-1 and are not transported to the hospital by ambulance. A follow-up survey of chest pain patients presenting to participating EDs in 20 US communities who were either released or admitted to the hospital with a confirmed coronary event revealed that the average proportion of patients who used EMS was 23%, with significant geographic difference (range 10% to 48%). Most patients were driven by someone else (60%) or drove themselves to the hospital (16%) (109). In the National Registry of Myocardial Infarction 2, just over half (53%) of all patients with MI were transported to the hospital by ambulance (105).

Even in areas of the country that have undertaken substantial public education campaigns about the warning signs of ACS and the need to activate the EMS system rapidly, either there were no increases in EMS use (58,110–113) or EMS use increased (as a secondary outcome measure) but was still suboptimal, with a 20% increase from a baseline of 33% in all 20 communities in the REACT study (63) and an increase from 27% to 41% in southern Minnesota after a community campaign (114). Given the importance of patients using EMS for possible acute cardiac symptoms, communities, including medical providers, EMS systems, health care insurers, hospitals, and policy makers at the state and local level, need to have agreed-upon emergency protocols to ensure patients with possible heart attack symptoms will be able to access 9-1-1 without barriers, to secure their timely evaluation and treatment (115).

As part of making a plan with the patient for timely recognition and response to an acute event, providers should review instructions for taking NTG in response to chest discomfort/pain (Fig. 3). If a patient has previously been prescribed NTG, it is recommended that the patient be advised to take 1 NTG dose sublingually promptly for chest discomfort/pain. If symptoms are unimproved or worsening 5 min after 1 NTG dose has been taken, it also is recommended that the patient be instructed to call 9-1-1 immediately to access EMS. Although the traditional recommendation is for patients to take 1 NTG dose sublingually, 5 min apart, for up to 3 doses before calling for emergency evaluation, this recommendation has been modified by the UA/NSTEMI Writing Committee to encourage earlier contacting of EMS by patients with symptoms suggestive of ACS. While awaiting ambulance arrival, patients tolerating NTG can be instructed by health care providers or 9-1-1 dispatchers to take additional NTG every 5 min up to 3 doses. Self-treatment with prescription medication, including nitrates, and with nonprescription medication (e.g., antacids) has been documented as a frequent cause of delay among patients with ACS, including those with a history of MI or angina (65,116). Both the rate

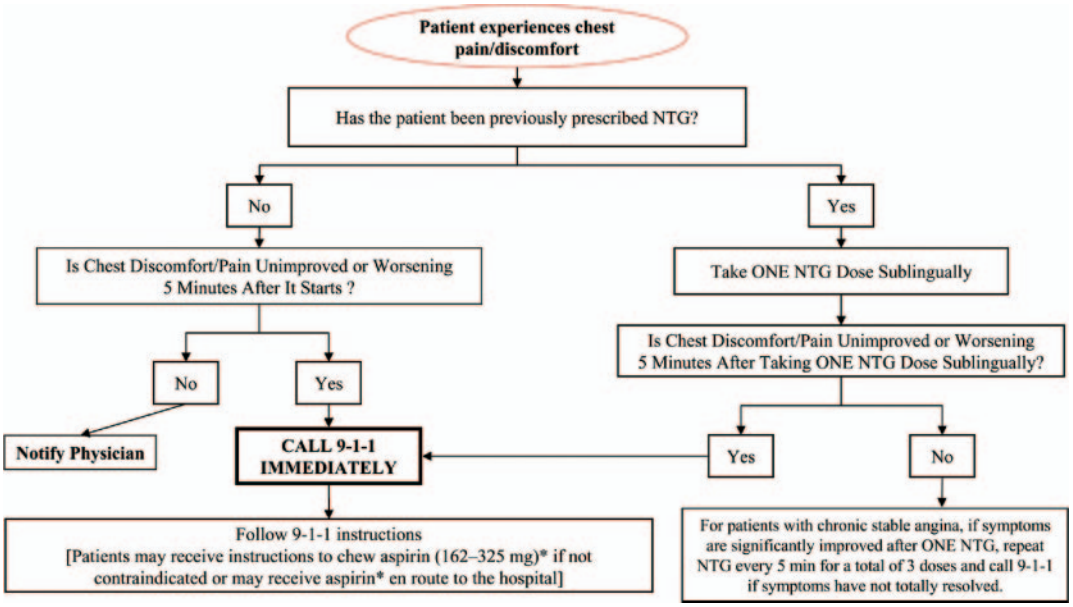


Figure 3. Patient (Advance) Instructions for NTG Use and EMS Contact in the Setting of Non–Trauma-Related Chest Discomfort/Pain

If patients experience chest discomfort/pain and have been previously prescribed NTG and have it available (right side of algorithm), it is recommended that they be instructed (in advance) to take 1 dose of NTG immediately in response to symptoms. If chest discomfort/pain is unimproved or worsening 5 min after taking 1 NTG sublingually, it is recommended that the patient call 9-1-1 immediately to access EMS. In patients with chronic stable angina, if the symptoms are significantly improved after taking 1 NTG, it is appropriate to instruct the patient or family member/friend/caregiver to repeat NTG every 5 min for a maximum of 3 doses and call 9-1-1 if symptoms have not totally resolved. If patients are not previously prescribed NTG (left side of algorithm), it is recommended that they call 9-1-1 if chest discomfort/pain is unimproved or worsening 5 min after it starts. If the symptoms subside within 5 min of when they began, patients should notify their physician of the episode. (For those patients with new-onset chest discomfort who have not been prescribed NTG, it is appropriate to discourage them from seeking someone else's NTG [e.g., from a neighbor, friend, or relative].) *Although some trials have used enteric-coated aspirin for initial dosing, more rapid buccal absorption occurs with non–enteric-coated formulations. EMS = emergency medical services; NTG = nitroglycerin.

of use of these medications and the number of doses taken were positively correlated with delay time to hospital arrival (65).

Family members, close friends, caregivers, or advocates should be included in these discussions and enlisted as reinforcement for rapid action when the patient experiences symptoms of a possible ACS (74,117,118) (Fig. 3). For patients known to their providers to have frequent angina, physicians may consider a selected, more tailored message that takes into account the frequency and character of the patient's angina and their typical time course of response to NTG. In many of these patients with chronic stable angina, if chest pain is significantly improved by 1 NTG, it is still appropriate to instruct the patient or family member/friend/caregiver to repeat NTG every 5 min for a maximum of 3 doses and to call 9-1-1 if symptoms have not resolved completely. Avoidance of patient delay associated with self-medication and prolonged reevaluation of symptoms are paramount. An additional consideration in high-risk CHD patients is to train family members in CPR and/or to have home access to an automatic external defibrillator, now available commercially to the public.

The taking of aspirin by patients in response to acute symptoms has been reported to be associated with a delay in calling EMS (109). Patients should focus on calling 9-1-1, which activates the EMS system, where they may receive instructions from emergency medical dispatchers to chew aspirin (162 to 325 mg) while emergency personnel are en route, or emergency personnel can give an aspirin while transporting the patient to the hospital (119). Alternatively, patients may receive an aspirin as part of their early treatment once they arrive at the hospital if it has not been given in the prehospital setting (117).

Providers should target those patients at increased risk for ACS, focusing on patients with known CHD, peripheral vascular disease, or cerebral vascular disease, those with diabetes, and patients with a 10-year Framingham risk of CHD of more than 20% (120). They should stress that the chest discomfort will usually not be dramatic, such as is commonly misrepresented on television or in the movies as a "Hollywood heart attack." Providers also should describe anginal equivalents and the commonly associated symptoms of ACS (e.g., shortness of breath, a cold sweat, nausea, or lightheadedness) in both men and women (56,106), as well as the increased frequency of atypical symptoms in elderly patients (72).

2.1.1. Emergency Department or Outpatient Facility Presentation

It is recommended that patients with a suspected ACS with chest discomfort or other ischemic symptoms at rest for more than 20 min, hemodynamic instability, or recent syncope or presyncope to be referred immediately to an ED or a specialized chest pain unit. For other patients with a suspected ACS who are experiencing less severe symptoms and are having none of the above high-risk features, the recommendation is to be seen initially in an ED, a chest pain unit, or an appropriate outpatient facility. Outcomes data that firmly support these recommendations are not available; however, these recommendations are of practical importance because differing ACS presentations require differing levels of emergent medical interventions, such as fibrinolytics or emergency coronary angiography leading to PCI or surgery, or sophisticated diagnostic evaluation such as nuclear stress testing or CCTA. When symptoms have been unremitting for more than 20 min, the possibility of MI must be considered. Given the strong evidence for a relationship between delay in treatment and death (121–123), an immediate assessment that includes a 12-lead ECG is essential. Patients who present with hemodynamic instability require an environment in which therapeutic interventions can be provided, and for those with presyncope or syncope, the major concern is the risk of sudden death. Such patients should be encouraged to seek emergency transportation when it is available. Transport as a passenger in a private vehicle is an acceptable alternative only if the wait for an emergency vehicle would impose a delay of greater than 20 to 30 min.

2.1.2. Questions to Be Addressed at the Initial Evaluation

The initial evaluation should be used to provide information about the diagnosis and prognosis. The attempt should be made to simultaneously answer 2 questions:

- What is the likelihood that the signs and symptoms represent ACS secondary to obstructive CAD (Table 6)?
- What is the likelihood of an adverse clinical outcome (Table 7)? Outcomes of concern include death, MI (or recurrent MI), stroke, HF, recurrent symptomatic ischemia, and serious arrhythmia.

For the most part, the answers to these questions form a sequence of contingent probabilities. Thus, the likelihood that the signs and symptoms represent ACS is contingent on the likelihood that the patient has underlying CAD. Similarly, the prognosis is contingent on the likelihood that the symptoms represent acute ischemia. However, in patients with symptoms of possible ACS, traditional risk factors for CAD are less important than are symptoms, ECG findings, and cardiac biomarkers. Therefore, the presence or absence of these traditional risk factors ordinarily should not be heavily weighed in determining whether an individual patient should be admitted or treated for ACS.

2.2. Early Risk Stratification

RECOMMENDATIONS FOR EARLY RISK STRATIFICATION

CLASS I

1. **A rapid clinical determination of the likelihood risk of obstructive CAD (i.e., high, intermediate, or low) should be made in all patients with chest discomfort or other symptoms suggestive of an ACS and considered in patient management.** ***(Level of Evidence: C)***

Table 6. Likelihood That Signs and Symptoms Represent an ACS Secondary to CAD

Feature	High Likelihood *Any of the following:*	Intermediate Likelihood *Absence of high-likelihood features and presence of any of the following:*	Low Likelihood *Absence of high- or intermediate-likelihood features but may have:*
History	Chest or left arm pain or discomfort as chief symptom reproducing prior documented angina Known history of CAD, including MI	Chest or left arm pain or discomfort as chief symptom Age greater than 70 years Male sex Diabetes mellitus	Probable ischemic symptoms in absence of any of the intermediate likelihood characteristics Recent cocaine use
Examination	Transient MR murmur, hypotension, diaphoresis, pulmonary edema, or rales	Extracardiac vascular disease	Chest discomfort reproduced by palpation
ECG	New, or presumably new, transient ST-segment deviation (1 mm or greater) or T-wave inversion in multiple precordial leads	Fixed Q waves ST depression 0.5 to 1 mm or T-wave inversion greater than 1 mm	T-wave flattening or inversion less than 1 mm in leads with dominant R waves Normal ECG
Cardiac markers	Elevated cardiac TnI, TnT, or CK-MB	Normal	Normal

Modified with permission from Braunwald E, Mark DB, Jones RH, et al. Unstable angina: diagnosis and management. Rockville, MD: Agency for Health Care Policy and Research and the National Heart, Lung, and Blood Institute, U.S. Public Health Service, U.S. Department of Health and Human Service, 1994. AHCPR publication no. 94-0602 (124).

ACS = acute coronary syndrome; CAD = coronary artery disease; CK-MB = MB fraction of creatine kinase; ECG = electrocardiogram; MI = myocardial infarction; MR = mitral regurgitation; TnI = troponin I; TnT = troponin T.

2. Patients who present with chest discomfort or other ischemic symptoms should undergo early risk stratification for the risk of cardiovascular events (e.g., death or [re]MI) that focuses on history, including anginal symptoms, physical findings, ECG findings, and biomarkers of cardiac injury, and results should be considered in patient management. *(Level of Evidence: C)*
3. A 12-lead ECG should be performed and shown to an experienced emergency physician as soon as possible after ED arrival, with a

Table 7. Short-Term Risk of Death or Nonfatal MI in Patients With UA/NSTEMI*

Feature	High Risk *At least 1 of the following features must be present:*	Intermediate Risk *No high-risk feature, but must have 1 of the following:*	Low Risk *No high- or intermediate-risk feature but may have any of the following features:*
History	Accelerating tempo of ischemic symptoms in preceding 48 h	Prior MI, peripheral or cerebrovascular disease, or CABG; prior aspirin use	
Character of pain	Prolonged ongoing (greater than 20 min) rest pain	Prolonged (greater than 20 min) rest angina, now resolved, with moderate or high likelihood of CAD Rest angina (greater than 20 min) or relieved with rest or sublingual NTG Nocturnal angina New-onset or progressive CCS class III or IV angina in the past 2 weeks without prolonged (greater than 20 min) rest pain but with intermediate or high likelihood of CAD (see Table 6)	Increased angina frequency, severity, or duration Angina provoked at a lower threshold New onset angina with onset 2 weeks to 2 months prior to presentation
Clinical findings	Pulmonary edema, most likely due to ischemia New or worsening MR murmur S_3 or new/worsening rales Hypotension, bradycardia, tachycardia Age greater than 75 years	Age greater than 70 years	
ECG	Angina at rest with transient ST-segment changes greater than 0.5 mm Bundle-branch block, new or presumed new Sustained ventricular tachycardia	T-wave changes Pathological Q waves or resting ST-depression less than 1 mm in multiple lead groups (anterior, inferior, lateral)	Normal or unchanged ECG
Cardiac markers	Elevated cardiac TnT, TnI, or CK-MB (e.g., TnT or TnI greater than 0.1 ng per ml)	Slightly elevated cardiac TnT, TnI, or CK-MB (e.g., TnT greater than 0.01 but less than 0.1 ng per ml)	Normal

*Estimation of the short-term risks of death and nonfatal cardiac ischemic events in UA (or NSTEMI) is a complex multivariable problem that cannot be fully specified in a table such as this; therefore, this table is meant to offer general guidance and illustration rather than rigid algorithms. Adapted from AHCPR Clinical Practice Guidelines No. 10, Unstable Angina: Diagnosis and Management, May 1994 (124).

CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; CK-MB = creatine kinase, MB fraction; ECG = electrocardiogram; MI = myocardial infarction; MR = mitral regurgitation; NTG = nitroglycerin; TnI = troponin I; TnT = troponin T; UA/NSTEMI = unstable angina/non–ST-elevation myocardial infarction.

goal of within 10 min of ED arrival for all patients with chest discomfort (or anginal equivalent) or other symptoms suggestive of ACS. *(Level of Evidence: B)*

4. If the initial ECG is not diagnostic but the patient remains symptomatic and there is high clinical suspicion for ACS, serial ECGs, initially at 15- to 30-min intervals, should be performed to detect the potential for development of ST-segment elevation or depression. *(Level of Evidence: B)*
5. Cardiac biomarkers should be measured in all patients who present with chest discomfort consistent with ACS. *(Level of Evidence: B)*
6. A cardiac-specific troponin is the preferred marker, and if available, it should be measured in all patients who present with chest discomfort consistent with ACS. *(Level of Evidence: B)*
7. Patients with negative cardiac biomarkers within 6 h of the onset of symptoms consistent with ACS should have biomarkers remeasured in the time frame of 8 to 12 h after symptom onset. (The exact timing of serum marker measurement should take into account the uncertainties often present with the exact timing of onset of pain and the sensitivity, precision, and institutional norms of the assay being utilized as well as the release kinetics of the marker being measured.) *(Level of Evidence: B)*
8. The initial evaluation of the patient with suspected ACS should include the consideration of noncoronary causes for the development of unexplained symptoms. *(Level of Evidence: C)*

CLASS IIa

1. Use of risk-stratification models, such as the Thrombolysis In Myocardial Infarction (TIMI) or Global Registry of Acute Coronary Events (GRACE) risk score or the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) risk model, can be useful to assist in decision making with regard to treatment options in patients with suspected ACS. *(Level of Evidence: B)*
2. It is reasonable to remeasure positive biomarkers at 6- to 8-h intervals 2 to 3 times or until levels have peaked, as an index of infarct size and dynamics of necrosis. *(Level of Evidence: B)*
3. It is reasonable to obtain supplemental ECG leads V_7 through V_9 in patients whose initial ECG is nondiagnostic to rule out MI due to left circumflex occlusion. *(Level of Evidence: B)*
4. Continuous 12-lead ECG monitoring is a reasonable alternative to serial 12-lead recordings in patients whose initial ECG is nondiagnostic. *(Level of Evidence: B)*

CLASS IIb

1. For patients who present within 6 h of the onset of symptoms consistent with ACS, assessment of an early marker of cardiac injury (e.g., myoglobin) in conjunction with a late marker (e.g., troponin) may be considered. *(Level of Evidence: B)*
2. For patients who present within 6 h of symptoms suggestive of ACS, a 2-h delta CK-MB mass in conjunction with 2-h delta troponin may be considered. *(Level of Evidence: B)*
3. For patients who present within 6 h of symptoms suggestive of ACS, myoglobin in conjunction with CK-MB mass or troponin when measured at baseline and 90 min may be considered. *(Level of Evidence: B)*
4. Measurement of B-type natriuretic peptide (BNP) or NT-pro-BNP may be considered to supplement assessment of global risk in patients with suspected ACS. *(Level of Evidence: B)*

CLASS III

Total CK (without MB), aspartate aminotransferase (AST, SGOT), alanine transaminase, beta-hydroxybutyric dehydrogenase, and/or lactate dehydrogenase should not be utilized as primary tests for the detection of myocardial injury in patients with chest discomfort suggestive of ACS. *(Level of Evidence: C)*

2.2.1. Estimation of the Level of Risk

The medical history, physical examination, ECG, assessment of renal function, and cardiac biomarker measurements in patients with symptoms suggestive of ACS at the time of the initial presentation can be integrated into an estimation of the risk of death and nonfatal cardiac ischemic events. The latter include new or recurrent MI, recurrent UA, disabling angina that requires hospitalization, and urgent coronary revascularization. Estimation of the level of risk is a multivariable problem that cannot be accurately quantified with a simple table; therefore, Tables 6 and 7 are meant to be illustrative of the general relationships between history, clinical and ECG findings, and the categorization of patients into those at low, intermediate, or high risk of the presence of obstructive CAD and the short-term risk of cardiovascular events, respectively. Optimal risk stratification requires accounting for multiple prognostic factors simultaneously by a multivariable approach (e.g., the TIMI and GRACE risk score algorithms [see below]).

2.2.2. Rationale for Risk Stratification

Because patients with ischemic discomfort at rest as a group are heterogeneous in terms of risk of cardiac death and nonfatal ischemic events, an assessment of the prognosis guides the initial evaluation and treatment. An estimation of risk is useful in 1) selection of the site of care (coronary care unit, monitored step-down unit, or outpatient setting) and 2) selection of therapy, including platelet glycoprotein (GP) IIb/IIIa inhibitors (see Section 3.2) and invasive management strategy (see Section 3.3). For all modes of presentation of an ACS, a strong relationship exists between indicators of the likelihood of ischemia due to CAD and prognosis (Tables 6 and 7). Patients with a high likelihood of ischemia due to CAD are at a greater risk of an untoward cardiac event than are patients with a lower likelihood of CAD. Therefore, an assessment of the likelihood of CAD is the starting point for the determination of prognosis in patients who present with symptoms suggestive of ACS. Other important elements for prognostic assessment are the tempo of the patient's clinical course, which relates to the short-term risk of future cardiac events, principally MI, and the patient's likelihood of survival should an MI occur.

Patients can present with ischemic discomfort but without ST-segment deviation on the 12-lead ECG in a variety of clinical scenarios, including no known prior history of CAD, a prior history of stable CAD, soon after MI, and after myocardial revascularization with CABG or PCI (12,125,126). As a clinical syndrome, ischemic discomfort without ST-segment elevation (UA and NSTEMI) shares

ill-defined borders with severe chronic stable angina, a condition associated with lower immediate risk, and STEMI, a presentation with a higher risk of early death and cardiac ischemic events. The risk is highest at the time of presentation and subsequently declines. Yet, the risk remains high past the acute phase. By 6 months, UA/NSTEMI mortality rates higher than that after STEMI can be seen (127); and by 12 months, the rates of death, MI, and recurrent instability in contemporary randomized controlled trials and registry studies exceed 10% and are often related to specific risk factors such as age, diabetes mellitus, renal failure, and impairment of left ventricular (LV) function. Whereas the early events are related to the activity of 1 culprit coronary plaque that has ruptured and is the site of thrombus formation, events that occur later are more related to the underlying pathophysiological mechanisms that trigger plaque activity and that mark active atherosclerosis (128–134).

A few risk scores have been developed that regroup markers of the acute thrombotic process and other markers of high risk to identify high-risk patients with UA/NSTEMI. The TIMI, GRACE, and PURSUIT risk scores are discussed in detail in Section 2.2.6.

2.2.3. History

Patients with suspected UA/NSTEMI may be divided into those with and those without a history of documented CAD. Particularly when the patient does not have a known history of CAD, the physician must determine whether the patient's presentation, with its constellation of specific symptoms and signs, is most consistent with chronic ischemia, acute ischemia, or an alternative disease process. The 5 most important factors derived from the initial history that relate to the likelihood of ischemia due to CAD, ranked in the order of importance, are 1) the nature of the anginal symptoms, 2) prior history of CAD, 3) sex, 4) age, and 5) the number of traditional risk factors present (135–139). In patients with suspected ACS but without preexisting clinical CHD, older age appears to be the most important factor. One study found that for males, age younger than 40 years, 40 to 55 years, and older than 55 years and for females, age younger than 50 years, 50 to 65 years, and older than 65 years was correlated with low, intermediate, and high risk for CAD, respectively (138). Another study found that the risk of CAD increased in an incremental fashion for each decade above age 40 years, with male sex being assigned an additional risk point (139,140). In these studies, being a male older than 55 years or a female older than 65 years outweighed the importance of all historical factors, including the nature of the chest pain (138,139).

2.2.4. Anginal Symptoms and Anginal Equivalents

The characteristics of angina, which are thoroughly described in the ACC/AHA 2002 Guideline Update for the Management of Patients With Chronic Stable Angina (4), include deep, poorly localized chest or arm discomfort that is reproducibly associated with physical exertion or emotional stress and is relieved promptly (i.e., in less than 5 min) with rest and/or the use of sublingual NTG. Patients with UA/NSTEMI may have discomfort that has all of the qualities of typical angina except that the episodes are more severe and prolonged, may occur at rest, or may be precipitated by less exertion than in the past. Although it is traditional to use the simple term "chest pain" to refer to the discomfort of ACS, patients often do not perceive these symptoms to be true pain, especially when they are mild or atypical. Terms such as "ischemic-type chest discomfort" or "symptoms suggestive of ACS" have been proposed to more precisely capture the character of ischemic symptoms. Although "chest discomfort" or "chest press" is frequently used in these guidelines for uniformity and brevity, the following caveats should be kept clearly in mind. Some patients may have no chest discomfort but present solely with jaw, neck, ear, arm, shoulder, back, or epigastric discomfort or with unexplained dyspnea without discomfort (56,141,142). If these symptoms have a clear relationship to exertion or stress or are relieved promptly with NTG, they should be considered equivalent to angina. Occasionally, such "anginal equivalents" that occur at rest are the mode of presentation of a patient with UA/NSTEMI, but without the exertional history or known prior history of CAD, it may be difficult to recognize their cardiac origin. Other difficult presentations of the patient with UA/NSTEMI include those without any chest (or equivalent) discomfort. Isolated unexplained new-onset or worsened exertional dyspnea is the most common anginal equivalent symptom, especially in older patients; less common isolated presentations, primarily in older adults, include nausea and vomiting, diaphoresis, and unexplained fatigue. Indeed, older adults and women with ACS not infrequently present with atypical angina or nonanginal symptoms. Rarely do patients with ACS present with syncope as the primary symptom or with other nonanginal symptoms.

Features that are not characteristic of myocardial ischemia include the following:

- Pleuritic pain (i.e., sharp or knifelike pain brought on by respiratory movements or cough)
- Primary or sole location of discomfort in the middle or lower abdominal region
- Pain that may be localized at the tip of 1 finger, particularly over the left ventricular apex or a costochondral junction
- Pain reproduced with movement or palpation of the chest wall or arms
- Very brief episodes of pain that last a few seconds or less
- Pain that radiates into the lower extremities

Documentation of the evaluation of a patient with suspected UA/NSTEMI should include the physician's opinion of whether the discomfort is in 1 of 3 categories: high, intermediate, or low likelihood of acute ischemia caused by CAD (Table 6).

Although typical characteristics substantially increase the probability of CAD, features not characteristic of typical angina, such as sharp stabbing pain or reproduction of pain on palpation, do not entirely exclude the possibility of ACS. In the Multicenter Chest Pain Study, acute ischemia was diagnosed in 22% of patients who presented to the ED with sharp or stabbing pain and in 13% of patients with pain with pleuritic qualities. Furthermore, 7% of patients whose pain was fully reproduced with palpation were ultimately recognized to have ACS (143). The Acute Cardiac Ischemia Time-Insensitive Predictive Instrument (ACI-TIPI) project (144,145) found that older age, male sex, the presence of chest or left arm pain, and the identification of chest pain or pressure as the most important presenting symptom all increased the likelihood that the patient was experiencing acute ischemia.

The relief of chest pain by administration of sublingual NTG in the ED setting is not always predictive of ACS. One study reported that sublingual NTG relieved symptoms in 35% of patients with active CAD (defined as elevated cardiac biomarkers, coronary vessel with at least 70% stenosis on coronary angiography, or positive stress test) compared with 41% of patients without active CAD (146). Furthermore, the relief of chest pain by the administration of a "GI cocktail" (e.g., a mixture of liquid antacid, viscous lidocaine, and anticholinergic agent) does not predict the absence of ACS (147).

2.2.5. Demographics and History in Diagnosis and Risk Stratification

In most studies of ACS, a prior history of MI has been associated not only with a high risk of obstructive CAD (148) but also with an increased risk of multivessel CAD. There are differences in the presentations of men and women with ACS (see Section 6.1). A smaller percentage of women than men present with STEMI, and of the patients who present without ST-segment elevation, fewer women than men have MIs (149). Women with suspected ACS are less likely to have obstructive CAD than are men with a similar clinical presentation, and when CAD is present in women, it tends to be less severe. On the other hand, when STEMI is present, the outcome in women tends to be worse even when adjustment is made for the older age and greater comorbidity of women. However, the outcome for women with UA is significantly better than the outcome for men, and the outcomes are similar for men and women with NSTEMI (150,151).

Older adults (see Section 6.4) have increased risks of both underlying CAD (152,153) and multivessel CAD; furthermore, they are at higher risk for an adverse outcome than are younger patients. The slope of the increased risk is steepest beyond age 70 years. This increased risk is related in part to the greater extent and severity of underlying CAD and the more severe LV dysfunction in older patients; however, age itself exerts a strong, independent prognostic risk as well, perhaps at least in part because of comorbidities. Older adults also are more likely to have atypical symptoms on presentation.

In patients with symptoms of possible ACS, some of the traditional risk factors for CAD (e.g., hypertension, hypercholesterolemia, and cigarette smoking) are only weakly predictive of the likelihood of acute ischemia (145,154) and are far less important than are symptoms, ECG findings, and cardiac biomarkers. Therefore, the presence or absence of these traditional risk factors ordinarily should not be used to determine whether an individual patient should be admitted or treated for ACS. However, the presence of these risk factors does appear to relate to poor outcomes in patients with established ACS. Although not as well investigated as the traditional risk factors, a family history of premature CAD has been demonstrated to be associated with increased coronary artery calcium scores greater than the 75th age percentile in asymptomatic individuals (155) and increased risk of 30-d cardiac events in patients admitted for UA/NSTEMI (156). Of special interest is that sibling history of premature CAD has a stronger relationship than parental history (157). However, several of these risk factors have important prognostic and therapeutic implications. Diabetes and the presence of extracardiac (carotid, aortic, or peripheral) vascular disease are major risk factors for poor outcome in patients with ACS (see Section 6.2). For both STEMI (158) and UA/NSTEMI (128), patients with these conditions have a significantly higher mortality rate and risk of acute HF. For the most part, this increase in risk is due to a greater extent of underlying CAD and LV dysfunction, but in many studies, diabetes carries prognostic significance over and above these findings. Similarly, a history of hypertension is associated with an increased risk of a poor outcome.

The current or prior use of ASA at the time and presentation of ACS has been associated in 1 database with increased cardiovascular event risk (159). Although the rationale is not fully elucidated, it appears those taking prior ASA therapy have more multivessel CAD, are more likely to present with thrombus present, may present later in the evolution of ACS, or may be ASA resistant. Surprisingly, current smoking is associated with a lower risk of death in the setting of ACS (159–161), primarily because of the younger age of smokers with ACS and less severe underlying CAD. This "smokers' paradox" seems to represent a tendency for smokers to develop thrombi on less severe plaques and at an earlier age than nonsmokers.

Being overweight and/or obese at the time of ACS presentation is associated with lower short-term risk of death; however, this "obesity paradox" is primarily a function of younger age at time of presentation, referral for angiography at an earlier stage of disease, and more aggressive ACS management (160). Although short-term risk may be lower for overweight/obese individuals, these patients have a higher long-term total mortality risk (161–165). Increased long-term cardiovascular risk appears to be primarily limited to severe obesity (166).

Cocaine use has been implicated as a cause of ACS, presumably owing to the ability of this drug to cause

coronary vasospasm and thrombosis in addition to its direct effects on heart rate and arterial pressure and its myocardial toxic properties (see Section 6.6) (167). Recently, the use of methamphetamine has grown, and its association with ACS also should be considered. It is important to inquire about the use of cocaine and methamphetamine in patients with suspected ACS, especially in younger patients (age less than 40 years) and others with few risk factors for CAD. Urine toxicology should be considered when substance abuse is suspected as a cause of or contributor to ACS.

2.2.6. Estimation of Early Risk at Presentation

A number of risk assessment tools have been developed to assist in assessing risk of death and ischemic events in patients with UA/NSTEMI, thereby providing a basis for therapeutic decision making (Table 8; Fig. 4) (158,168,169). It should be recognized that the predictive ability of these commonly used risk assessment scores for nonfatal CHD risk is only moderate.

Antman et al. developed the TIMI risk score (159), a simple tool composed of 7 (1-point) risk indicators rated on presentation (Table 8). The composite end points (all-cause mortality, new or recurrent MI, or severe recurrent ischemia prompting urgent revascularization within 14 d) increase as the TIMI risk score increases. The TIMI risk score has been validated internally within the TIMI 11B trial and 2 separate cohorts of patients from the Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and Non-Q-Wave Myocardial Infarction (ESSENCE) trial (169). The model remained a significant predictor of events and appeared relatively insensitive to missing information, such as knowledge of previously documented coronary stenosis of 50% or more. The model's predictive ability remained intact with a cutoff of 65 years of age. The TIMI risk score was recently studied in an unselected ED population with chest pain syndrome; its performance was similar to that in the ACS population in which it was derived and validated (170). The TIMI risk calculator is available at www.timi.org. The TIMI risk index, a modification of the TIMI risk score that uses the variables age, systolic blood pressure, and heart rate, has not only been shown to predict short-term mortality in STEMI but has also been useful in the prediction of 30-d and 1-year mortality across the spectrum of patients with ACS, including UA/NSTEMI (171).

Table 8. TIMI Risk Score for Unstable Angina/Non–ST-Elevation MI

TIMI Risk Score	All-Cause Mortality, New or Recurrent MI, or Severe Recurrent Ischemia Requiring Urgent Revascularization Through 14 d After Randomization, %
0–1	4.7
2	8.3
3	13.2
4	19.9
5	26.2
6–7	40.9

The TIMI risk score is determined by the sum of the presence of 7 variables at admission; 1 point is given for each of the following variables: age 65 y or older; at least 3 risk factors for CAD; prior coronary stenosis of 50% or more; ST-segment deviation on ECG presentation; at least 2 anginal events in prior 24 h; use of aspirin in prior 7 d; elevated serum cardiac biomarkers. Prior coronary stenosis of 50% or more remained relatively insensitive to missing information and remained a significant predictor of events. Reprinted with permission from Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. JAMA 2000;284:835–42 (159). Copyright © 2000 American Medical Association.

CAD = coronary artery disease; ECG = electrocardiogram; MI = myocardial infarction; y = year.

The PURSUIT risk model, developed by Boersma et al. (172), based on patients enrolled in the PURSUIT trial, is another useful tool to guide the clinical decision-making process when the patient is admitted to the hospital. In the PURSUIT risk model, critical clinical features associated with an increased 30-d incidence of death and the composite of death or myocardial (re)infarction were (in order of strength) age, heart rate, systolic blood pressure, ST-segment depression, signs of HF, and cardiac biomarkers (172).

The GRACE risk model, which predicts in-hospital mortality (and death or MI), can be useful to clinicians to guide treatment type and intensity (168,173). The GRACE risk tool was developed on the basis of 11,389 patients in GRACE, validated in subsequent GRACE and GUSTO IIb cohorts, and predicts in-hospital death in patients with STEMI, NSTEMI, or UA (C statistic = 0.83). The 8 variables used in the GRACE risk model are older age (odds ratio [OR] 1.7 per 10 years), Killip class (OR 2.0 per class), systolic blood pressure (OR 1.4 per 20 mm Hg decrease), ST-segment deviation (OR 2.4), cardiac arrest during presentation (OR 4.3), serum creatinine level (OR 1.2 per 1-mg per dL increase), positive initial cardiac biomarkers (OR 1.6), and heart rate (OR 1.3 per 30-beat per min increase). The sum of scores is applied to a reference monogram to determine the corresponding all-cause mortality from hospital discharge to 6 mo. The GRACE clinical application tool can be downloaded to a handheld PDA to be used at the bedside and is available at www.outcomes-umassmed.org/grace (Fig. 4) (173). An analysis comparing the 3 risk scores (TIMI, GRACE, and PURSUIT) concluded that all 3 demonstrated good predictive accuracy for death and MI at 1 year, thus identifying patients who might be likely to benefit from aggressive therapy, including early myocardial revascularization (174).

The ECG provides unique and important diagnostic and prognostic information (see also Section 2.2.6.1 below). Accordingly, ECG changes have been incorporated into quantitative decision aids for the triage of patients presenting with chest discomfort (175). Although ST elevation carries the highest early risk of death, ST depression on the presenting ECG portends the highest risk of death at 6 months, with the degree of ST depression showing a strong relationship to outcome (176).

Dynamic risk modeling is a new frontier in modeling that accounts for the common observation that levels and predictors of risk constantly evolve as patients pass through their disease process. Excellent models have been developed based on presenting features, but information the next day

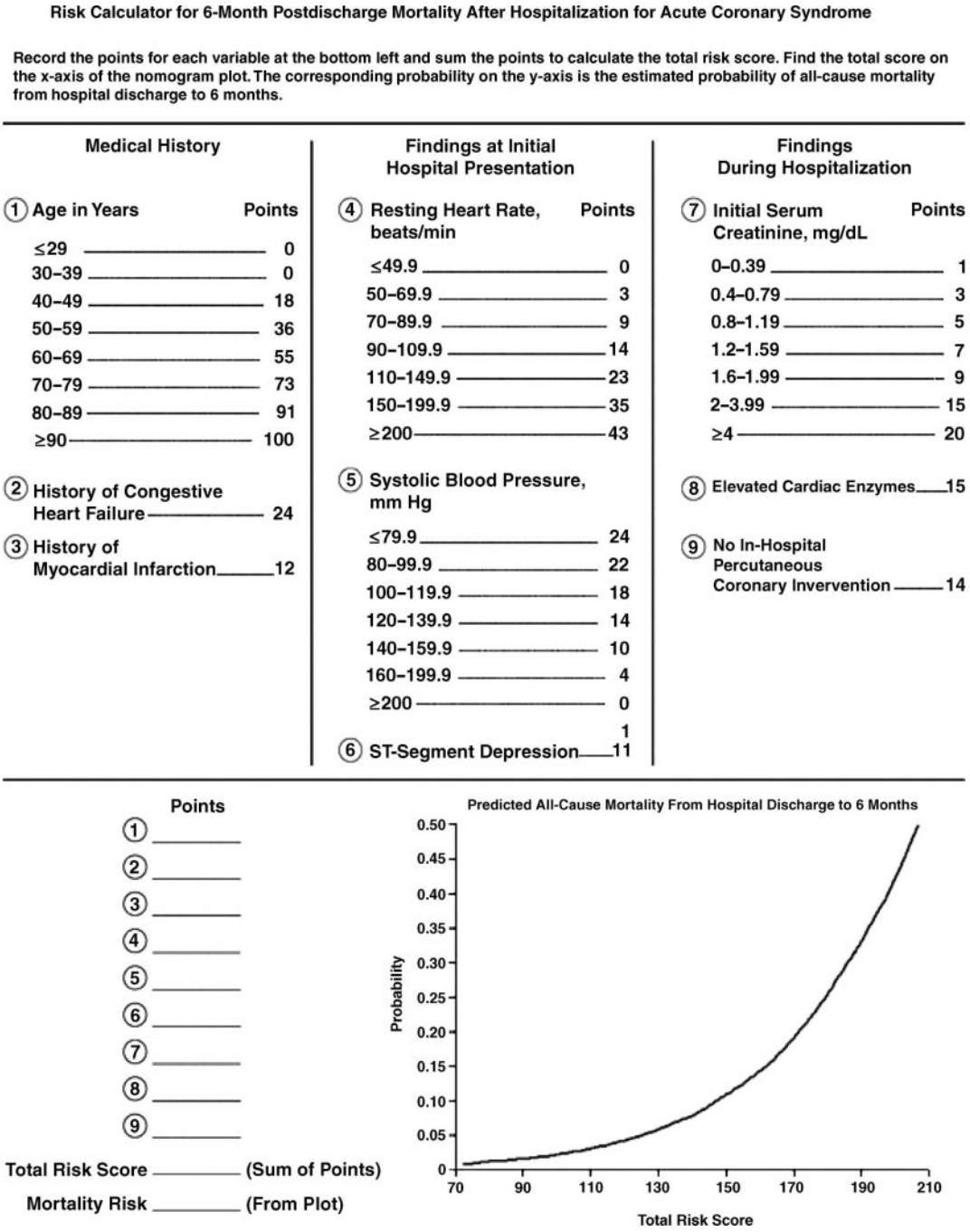


Figure 4. GRACE Prediction Score Card and Nomogram for All-Cause Mortality From Discharge to 6 Months

Reprinted with permission from Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. JAMA 2004;291:2727–33 (168). Copyright © 2004 American Medical Association.

about clinical (e.g., complications), laboratory (e.g., biomarker evolution), and ECG (e.g., ST resolution for STEMI) changes provides additional data relevant to decisions at key "decision-node" points in care (177). Dynamic modeling concepts promise more sophisticated, adaptive, and individually predictive modeling of risk in the future.

Renal impairment has been recognized as an additional high-risk feature in patients with ACS (178). Mild to moderate renal dysfunction is associated with moderately increased short- and long-term risks, and severe renal dysfunction is associated with severely increased short- and long-term mortality risks. Patients with renal dysfunction

experience increased bleeding risks, have higher rates of HF and arrhythmias, have been underrepresented in cardiovascular trials, and may not enjoy the same magnitude of benefit with some therapies observed in patients with normal renal function (179) (see also Section 6.5).

Among patients with UA/NSTEMI, there is a progressively greater benefit from newer, more aggressive therapies such as low-molecular-weight heparin (LMWH) (169,180), platelet GP IIb/IIIa inhibition (181), and an invasive strategy (182) with increasing risk score.

2.2.6.1. ELECTROCARDIOGRAM

The ECG is critical not only to add support to the clinical suspicion of CAD but also to provide prognostic information based on the pattern and magnitude of the abnormalities (127,175,183,184). A recording made during an episode of the presenting symptoms is particularly valuable. Importantly, transient ST-segment changes (greater than or equal to 0.05 mV [i.e., 0.5 mm]) that develop during a symptomatic episode at rest and that resolve when the patient becomes asymptomatic strongly suggest acute ischemia and a very high likelihood of underlying severe CAD. Patients whose current ECG suggests ischemia can be assessed with greater diagnostic accuracy if a prior ECG is available for comparison (Table 6) (185).

Although it is imperfect, the 12-lead ECG lies at the center of the decision pathway for the evaluation and management of patients with acute ischemic discomfort (Fig. 1; Table 6). The diagnosis of MI is confirmed with serial cardiac biomarkers in more than 90% of patients who present with ST-segment elevation of greater than or equal to 1 mm (0.1 mV) in at least 2 contiguous leads, and such patients should be considered candidates for acute reperfusion therapy. Patients who present with ST-segment depression are initially considered to have either UA or NSTEMI; the distinction between the 2 diagnoses is ultimately based on the detection of markers of myocardial necrosis in the blood (11,126,186).

Up to 25% of patients with NSTEMI and elevated CK-MB go on to develop Q-wave MI during their hospital stay, whereas the remaining 75% have non–Q-wave MI. Acute fibrinolytic therapy is contraindicated for ACS patients without ST-segment elevation, except for those with electrocardiographic true posterior MI manifested as ST-segment depression in 2 contiguous anterior precordial leads and/or isolated ST-segment elevation in posterior chest leads (187–189). Inverted T waves may also indicate UA/NSTEMI. In patients suspected of having ACS on clinical grounds, marked (greater than or equal to 2 mm [0.2 mV]) symmetrical precordial T-wave inversion strongly suggests acute ischemia, particularly that due to a critical stenosis of the left anterior descending coronary artery (LAD) (190). Patients with this ECG finding often exhibit hypokinesis of the anterior wall and are at high risk if given medical treatment alone (191). Revascularization will often reverse both the T-wave inversion and wall-motion disorder (192). Nonspecific ST-segment and T-wave changes, usually defined as ST-segment deviation of less than 0.5 mm (0.05 mV) or T-wave inversion of less than or equal to 2 mm (0.2 mV), are less diagnostically helpful than the foregoing findings. Established Q waves greater than or equal to 0.04 s are also less helpful in the diagnosis of UA, although by suggesting prior MI, they do indicate a high likelihood of significant CAD. Isolated Q waves in lead III may be a normal finding, especially in the absence of repolarization abnormalities in any of the inferior leads. A completely normal ECG in a patient with chest pain does not exclude the possibility of ACS, because 1% to 6% of such patients eventually are proved to have had an MI (by definition, an NSTEMI), and at least 4% will be found to have UA (184,193,194).

The common alternative causes of ST-segment and T-wave changes must be considered. In patients with ST-segment elevation, the diagnoses of LV aneurysm, pericarditis, myocarditis, Prinzmetal's angina, early repolarization (e.g., in young black males), apical LV ballooning syndrome (Takotsubo cardiomyopathy; see Section 6.9), and Wolff-Parkinson-White syndrome represent several examples to be considered. Central nervous system events and drug therapy with tricyclic antidepressants or phenothiazines can cause deep T-wave inversion.

Acute MI due to occlusion of the left circumflex coronary artery can present with a nondiagnostic 12-lead ECG. Approximately 4% of acute MI patients show the presence ST elevation isolated to the posterior chest leads V_7 through V_9 and "hidden" from the standard 12 leads (187,195,196). The presence of posterior ST elevation is diagnostically important because it qualifies the patient for acute reperfusion therapy as an acute STEMI (1,197). The presence or absence of ST-segment elevation in the right ventricular (V_4R through V_6R) or posterior chest leads (V_7 through V_9) also adds prognostic information in the presence of inferior ST-segment elevation, predicting high and low rates of in-hospital life-threatening complications, respectively (196).

With reference to electrocardiographic true posterior MI, new terminology recently has been proposed based on the standard of cardiac magnetic resonance (CMR) imaging localization. CMR studies indicate that abnormally increased R waves, the Q-wave equivalent in leads V_1 and V_2, indicate an MI localized to the lateral LV wall and that abnormal Q waves in I and VL (but not V_6) indicate a mid-anterior wall MI. Thus, the electrocardiographic terms "posterior" and "high lateral MI" refer to anatomic "lateral wall MI" and "mid-anterior wall MI" (198). The impact of these findings and recommendations for standard electrocardiographic terminology are unresolved as of this writing.

Several investigators have shown that a gradient of risk of death and cardiac ischemic events can be established based on the nature of the ECG abnormality (183,199,200). Patients with ACS and confounding ECG patterns such as

bundle-branch block, paced rhythm, or LV hypertrophy are at the highest risk for death, followed by patients with ST-segment deviation (ST-segment elevation or depression); at the lowest risk are patients with isolated T-wave inversion or normal ECG patterns. Importantly, the prognostic information contained within the ECG pattern remains an independent predictor of death even after adjustment for clinical findings and cardiac biomarker measurements (199–202).

In addition to the presence or absence of ST-segment deviation or T-wave inversion patterns as noted earlier, there is evidence that the magnitude of the ECG abnormality provides important prognostic information. Thus, Lloyd-Jones et al. (203) reported that the diagnosis of acute non–Q-wave MI was 3 to 4 times more likely in patients with ischemic discomfort who had at least 3 ECG leads that showed ST-segment depression and maximal ST depression of greater than or equal to 0.2 mV. Investigators from the TIMI III Registry (199) reported that the 1-year incidence of death or new MI in patients with at least 0.5 mm (0.05 mV) of ST-segment deviation was 16.3% compared with 6.8% for patients with isolated T-wave changes and 8.2% for patients with no ECG changes.

Physicians frequently seek out a previous ECG for comparison in patients with suspected ACS. Studies have demonstrated that patients with an unchanged ECG have a reduced risk of MI and a very low risk of in-hospital life-threatening complications even in the presence of confounding ECG patterns such as LV hypertrophy (204–206).

Because a single 12-lead ECG recording provides only a snapshot view of a dynamic process (207), the usefulness of obtaining serial ECG tracings or performing continuous ST-segment monitoring has been studied (175,208). Although serial ECGs increase the ability to diagnose UA and MI (208–212), the yield is higher with serial cardiac biomarker measurements (212–214). However, identification of new injury on serial 12-lead ECG (and not elevated cardiac biomarkers) is the principal eligibility criterion for emergency reperfusion therapy, so that monitoring of both is recommended. Continuous 12-lead ECG monitoring to detect ST-segment shifts, both symptomatic and asymptomatic, also can be performed with microprocessor-controlled programmable devices. An injury current was detected in an additional 16% of chest pain patients in 1 study (213). The identification of ischemic ECG changes on serial or continuous ECG recordings frequently alters therapy and provides independent prognostic information (212,215,216).

2.2.6.2. PHYSICAL EXAMINATION

The major objectives of the physical examination are to identify potential precipitating causes of myocardial ischemia, such as uncontrolled hypertension, thyrotoxicosis, or gastrointestinal bleeding, and comorbid conditions that could impact therapeutic risk and decision making, such as pulmonary disease and malignancies, as well as to assess the hemodynamic impact of the ischemic event. Every patient with suspected ACS should have his or her vital signs measured (blood pressure in both arms if dissection is suspected, as well as heart rate and temperature) and should undergo a thorough cardiovascular and chest examination. Patients with evidence of LV dysfunction on examination (rales, S_3 gallop) or with acute mitral regurgitation have a higher likelihood of severe underlying CAD and are at a high risk of a poor outcome. Just as the history of extracardiac vascular disease is important, the physical examination of the peripheral vessels can also provide important prognostic information. The presence of bruits or pulse deficits that suggest extracardiac vascular disease identifies patients with a higher likelihood of significant CAD.

Elements of the physical examination can be critical in making an important alternative diagnosis in patients with chest pain. In particular, several disorders carry a significant threat to life and function if not diagnosed acutely. Aortic dissection is suggested by pain in the back, unequal pulses, or a murmur of aortic regurgitation. Acute pericarditis is suggested by a pericardial friction rub, and cardiac tamponade can be evidenced by pulsus paradoxus. Pneumothorax is suspected when acute dyspnea, pleuritic chest pain, and differential breath sounds are present.

The importance of cardiogenic shock in patients with NSTEMI should be emphasized. Although most literature on cardiogenic shock has focused on STEMI, the SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK (SHOCK) study (217) found that approximately 20% of all cardiogenic shock complicating MI was associated with NSTEMI. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO)-II (218) and PURSUIT (128) trials found that cardiogenic shock occurs in up to 5% of patients with NSTEMI and that mortality rates are greater than 60%. Thus, hypotension and evidence of organ hypoperfusion can occur and constitute a medical emergency in NSTEMI.

2.2.7. Noncardiac Causes of Symptoms and Secondary Causes of Myocardial Ischemia

Information from the initial history, physical examination, and ECG (Table 6) can enable the physician to classify and exclude from further assessment patients "not having ischemic discomfort." This includes patients with noncardiac pain (e.g., pulmonary embolism, musculoskeletal pain, or esophageal discomfort) or cardiac pain not caused by myocardial ischemia (e.g., acute pericarditis). The remaining patients should undergo a more complete evaluation of the secondary causes of UA that might alter management. This evaluation should include a physical examination for evidence of other cardiac disease, an ECG to screen for arrhythmias, measurement of body temperature and blood pressure, and determination of hemoglobin or hematocrit. Cardiac disorders other than CAD that can cause myocardial ischemia include aortic stenosis and hypertrophic car-

diomyopathy. Factors that increase myocardial oxygen demand or decrease oxygen delivery to the heart can provoke or exacerbate ischemia in the presence of significant underlying CAD or secondary angina; previously unrecognized gastrointestinal bleeding that causes anemia is a common secondary cause of worsening angina or the development of symptoms of ACS. Acute worsening of chronic obstructive pulmonary disease (with or without superimposed infection) can lower oxygen saturation levels sufficiently to intensify ischemic symptoms in patients with CAD. Evidence of increased cardiac oxygen demand can be suspected in the presence of fever, signs of hyperthyroidism, sustained tachyarrhythmias, or markedly elevated blood pressure. Another cause of increased myocardial oxygen demand is arteriovenous fistula in patients receiving dialysis.

The majority of patients seen in the ED with symptoms of possible ACS will be judged after their workup not to have a cardiac problem. One clinical trial of a predictive instrument evaluated 10,689 patients with suspected ACS (75). To participate, patients were required to be greater than 30 years of age with a chief symptom of chest, left arm, jaw, or epigastric pain or discomfort; shortness of breath; dizziness; palpitations; or other symptoms suggestive of acute ischemia. After evaluation, 7,996 patients (75%) were deemed not to have acute ischemia.

2.2.8. Cardiac Biomarkers of Necrosis and the Redefinition of AMI

Cardiac biomarkers have proliferated over recent years to address various facets of the complex pathophysiology of ACS. Some, like the cardiac troponins, have become essential for risk stratification of patients with UA/NSTEMI and for the diagnosis of MI. Others, such as the inflammatory markers, are opening new perspectives on pathophysiology and risk stratification, and the use in clinical practice of selected new markers may be recommended for clinical use in the near future. Still other promising markers are being developed as part of translational research and await prospective validation in various populations. New developments are expected in the fields of proteomic and genomics, cell markers and circulating microparticles, and microtechnology and nanotechnology imaging.

Current markers of necrosis leak from cardiomyocytes after the loss of membrane integrity and diffuse into the cardiac interstitium, then into the lymphatics and cardiac microvasculature. Eventually, these macromolecules, collectively referred to as cardiac biomarkers, are detectable in the peripheral circulation. Features that favor their diagnostic performance are high concentrations in the myocardium and absence in nonmyocardial tissue, release into the blood within a convenient diagnostic time window and in proportion to the extent of myocardial injury, and quantification with reproducible, inexpensive, and rapid and easily applied assays (11). The cardiac troponins possess many of these features and have gained wide acceptance as the biomarkers of choice in the evaluation of patients with ACS for diagnosis, risk stratification, and treatment selection.

The traditional definitions of MI were revisited in 2000 in a consensus document of a joint committee of the European Society of Cardiology (ESC) and ACC (219) and at the time of publication is being updated by an expanded joint task force of the ESC, ACC, AHA, World Heart Federation (WHF), and World Health Organization. The new definitions are inspired by the emergence of new highly sensitive and specific diagnostic methods that allow the detection of areas of cell necrosis as small as 1 g. Myocardial necrosis in the task force document is defined by an elevation of troponin above the 99th percentile of normal. Myocardial infarction, which is necrosis related to ischemia, is further defined by the addition to the troponin elevation of at least 1 of the following criteria: ischemic ST and T-wave changes, new left bundle-branch block, new Q waves, PCI-related marker elevation, or positive imaging for a new loss of viable myocardium. Myocardial infarction can still be diagnosed in the absence of measurement of troponin when there is evidence of a new loss of viable myocardium, ST-segment elevation, or new left bundle-branch block with sudden cardiac death within 1 h of symptoms, or a postmortem pathological diagnosis. Coronary artery bypass graft-related MI is diagnosed by an increase of cardiac biomarkers to more than 5 to 10-fold the 99th percentile of normal, new Q waves or new left bundle-branch block on the ECG, or a positive imaging test. The task force further recommended further defining MI by the circumstances that cause it (spontaneous or in the setting of a diagnostic or therapeutic procedure), by the amount of cell loss (infarct size), and by the timing of MI (evolving, healing, or healed) (219,220). Providing fold-elevations above normal for diagnostic biomarkers, to allow for meaningful comparisons among clinical trials, is also endorsed.

At the present time, the implications of using the new ESC/ACC redefinition of MI have not been fully explored; much of the present database for UA/NSTEMI derives from CK/CK-MB–based definitions of MI. Moreover, troponin assays have rapidly evolved through several generations over the past decade, becoming increasingly more sensitive and specific. Thus, it is important to recognize that the recommendations in this section are formulated from studies that frequently utilize modified World Health Organization criteria or definitions of MI based on earlier-generation troponin assays.

2.2.8.1. CREATINE KINASE-MB

Creatine kinase-MB, a cytosolic carrier protein for high-energy phosphates, has long been the standard marker for the diagnosis of MI. Creatine kinase-MB, however, is less sensitive and less specific for MI than the cardiac troponins. Low levels of CK-MB can be found in the blood of healthy persons, and elevated levels occur with damage to skeletal muscle (221).

When a cardiac troponin is available, the determination of CK-MB remains useful in a few specific clinical situations. One is the diagnosis of early infarct extension (reinfarction), because the short half-life of CK-MB compared with troponin permits the detection of a diagnostic new increase after initial peak. Although routine determination of CK-MB has been suggested for the diagnosis of an eventual infarct extension, a single CK-MB determination obtained when symptoms recur may serve as the baseline value for comparison with samples obtained 6 to 12 h later. Another situation is the diagnosis of a periprocedural MI, because the diagnostic and prognostic value of CK-MB in these situations has been extensively validated. When assessed, CK-MB should be measured by mass immunoassays and not by other methods previously used (222). The use of other, older biochemistry assays of nonspecific markers such as alanine transaminase, aspartate transaminase, and lactate dehydrogenase should generally be avoided in contemporary practice.

2.2.8.2. CARDIAC TROPONINS

The troponin complex consists of 3 subunits: T (TnT), I (TnI), and C (TnC) (223). The latter is expressed by both cardiac and skeletal muscle, whereas TnT and TnI are derived from heart-specific genes. Therefore, the term "cardiac troponins" (cTn) in these guidelines refers specifically to either cTnT or cTnI. Cardiac troponin as a biomarker provides robust results that are highly sensitive and specific in detecting cell necrosis; an early release is attributable to a cytosolic pool and a late release to the structural pool (219,224).

Because cTnT and cTnI generally are not detected in the blood of healthy persons, the cutoff value for elevated cTnT and cTnI levels may be set to slightly above the upper limit of the performance characteristics of the assay for a normal healthy population. High-quality analytic methods are needed to achieve these high standards (225). One issue with the use of cTnI is the multiplicity of existing assays that have different analytical sensitivities, some being unable to detect the lower values with a reasonable precision (226). Physicians therefore need to know the sensitivity of the tests used for TnI in their hospitals at the cutoff concentrations used for clinical decisions. Such heterogeneity does not exist for cTnT, which exists as a single test; this test is now a third-generation immunoassay that uses recombinant monoclonal human antibodies (224). Rare patients may have blocking antibodies to part of the troponin molecule, which would result in false-negative results (227).

2.2.8.2.1. CLINICAL USE

Although troponins can be detected in blood as early as 2 to 4 h after the onset of symptoms, elevation can be delayed for up to 8 to 12 h. This timing of elevation is similar to that of CK-MB but persists longer, for up to 5 to 14 d (Fig. 5). An increasing pattern in serial levels best helps determine whether the event is acute, distinct from a previous event, subacute, or chronic.

The proportion of patients showing a positive cTn value depends on the population of patients under evaluation. Approximately 30% of patients with typical rest chest discomfort without ST-segment elevation who would be diagnosed as having UA because of a lack of CK-MB elevation actually have NSTEMI when assessed with cardiac-specific troponin assays. The diagnosis of MI in the community at large when cTn is used results in a large increase in the incidence of MIs, by as much as 41% compared with use of only CK-MB alone, and a change in the case mix, with a survival rate that is better than that of MI identified by the previous criteria (228). Troponin elevation conveys prognostic information beyond that supplied by the clinical characteristics of the patient, the ECG at presentation, and the predischarge exercise test (200,201,229–231). Furthermore, a quantitative relationship exists between the amount of elevation of cTn and the risk of death (200,201) (Fig. 6). The incremental risk of death or MI in troponin-positive versus troponin-negative patients is summarized in Table 9. It should be cautioned, however, that cTn should not be used as the sole marker of risk, because patients without troponin elevations can still have a substantial risk of an adverse outcome.

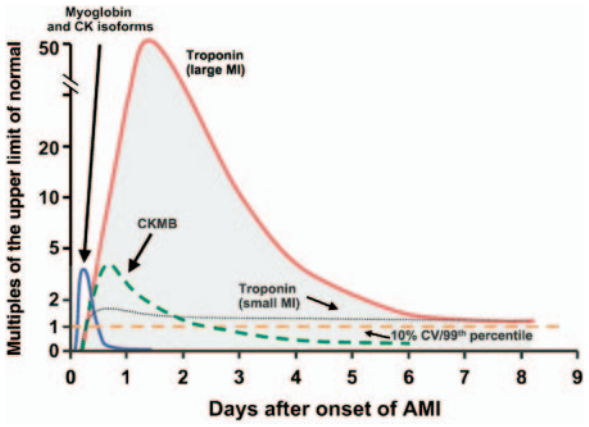


Figure 5. Timing of Release of Various Biomarkers After Acute Myocardial Infarction

The biomarkers are plotted showing the multiples of the cutoff for acute myocardial infarction (AMI) over time. The dashed horizontal line shows the upper limit of normal (ULN; defined as the 99th percentile from a normal reference population without myocardial necrosis; the coefficient of variation of the assay should be 10% or less). The earliest rising biomarkers are myoglobin and CK isoforms (leftmost curve). CKMB (dashed curve) rises to a peak of 2 to 5 times the ULN and typically returns to the normal range within 2 to 3 d after AMI. The cardiac-specific troponins show small elevations above the ULN in small infarctions (e.g., as is often the case with NSTEMI) but rise to 20 to 50 times the ULN in the setting of large infarctions (e.g., as is typically the case in STEMI). The troponin levels may stay elevated above the ULN for 7 d or more after AMI. Modified from Shapiro BP, Jaffe AS. Cardiac biomarkers. In: Murphy JG, Lloyd MA, editors. *Mayo Clinic Cardiology: Concise Textbook*. 3rd ed. Rochester, MN: Mayo Clinic Scientific Press and New York: Informa Healthcare USA, 2007:773–80 (70). Used with permission of Mayo Foundation for Medical Education and Research. CK = creatine kinase; CKMB = MB fraction of creatine kinase; CV = coefficient of variation; MI = myocardial infarction; NSTEMI = non–ST-elevation myocardial infarction; UA/NSTEMI = unstable angina/non–ST-elevation myocardial infarction.

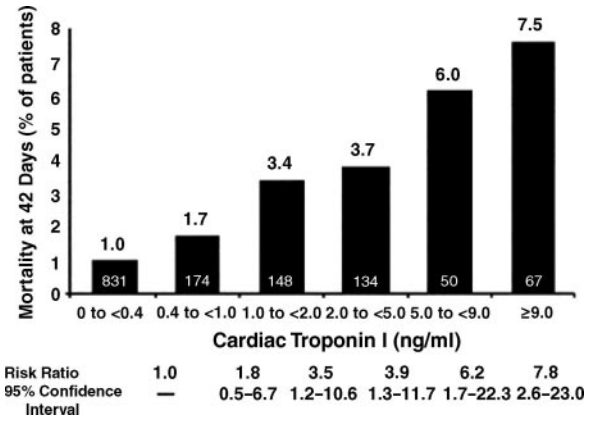


Figure 6. Troponin I Levels to Predict the Risk of Mortality in Acute Coronary Syndromes

Mortality rates are at 42 d (without adjustment for baseline characteristics) in patients with acute coronary syndrome. The numbers at the bottom of each bar are the numbers of patients with cardiac troponin I levels in each range, and the numbers above the bars are percentages. p less than 0.001 for the increase in the mortality rate (and the risk ratio for mortality) with increasing levels of cardiac troponin I at enrollment. Reprinted with permission from Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 1996;335:1342–9 (201).

Although cTn accurately identifies myocardial necrosis, it does not inform as to the cause or causes of necrosis; these can be multiple (224) and include noncoronary causes such as tachyarrhythmia, cardiac trauma by interventions, chest trauma from motor vehicle accidents, HF, LV hypertrophy, myocarditis, and pericarditis, as well as severe noncardiac conditions such as sepsis, burns, respiratory failure, acute neurological diseases, pulmonary embolism, pulmonary hypertension, drug toxicity, cancer chemotherapy, and renal insufficiency (230). Therefore, in making the diagnosis of NSTEMI, cTns should be used in conjunction with other criteria of MI, including characteristics of the ischemic symptoms and the ECG.

In all of these situations, equivalent information is generally obtained with cTnI and cTnT, except in patients with renal dysfunction, in whom cTnI assessment appears to have a specific role (227). Among patients with end-stage renal disease and no clinical evidence of acute myocardial necrosis, 15% to 53% show increased cTnT, but fewer than 10% have increased cTnI; dialysis generally increases cTnT but decreases cTnI. The exact reasons for the high rates of elevation in the cTn, especially cTnT, in renal failure are not clear; they can relate to cardiac damage, differential clearance, or to other biochemical or metabolic abnormalities (227). Whatever the reasons and the sources, an elevation of cTn, including cTnT, in patients with renal insufficiency is associated with a higher risk of morbidity regardless of the presence of cardiac symptoms or documented CAD. Among 7,033 patients enrolled in the GUSTO IV trial with suspected ACS, TnT level was independently predictive of risk across the entire spectrum of renal function enrolled (233).

Aggressive preventive measures for patients with renal insufficiency have been suggested, because most deaths in renal failure are of cardiac origin (227). Unfortunately, some standard therapies, such as lipid lowering with statins or PCI, have been less effective in improving survival in certain patient populations with advanced renal insufficiency (234,235). Furthermore, patients with suspected UA/NSTEMI have particularly unfavorable outcomes when in renal failure, with an event rate that correlates with the decrease in creatinine clearance (236–239). A sequential change in cTn levels in the first 24 h of observation for a suspected ACS supports new myocardial injury, whereas unchanging levels are more consistent with a chronic disease state without ACS.

Table 9. Risk of Death Associated With a Positive Troponin Test in Patients With Suspected ACS

Subgroup	Events/Total		Summary RR	95% CI	No. of Studies
	Negative Troponin	Positive Troponin			
TnT					
Total death	32/1,187	46/473	3.1	2.0 to 4.9	5
Cardiac death	31/1,689	52/744	3.8	2.4 to 6.0	7
UA patients*	21/397	26/198	2.5	1.4 to 4.5	5
Chest pain patients*	43/2,479	73/1,019	4.0	2.7 to 5.9	7
TnI					
Total death	34/1,451	49/815	3.1	2.0 to 4.9	3
Cardiac death	3/905	26/384	25.0	11 to 55	2
UA patients*	2/70	2/22	3.2	0.3 to 40	1
Chest pain patients*	35/2,286	73/1,177	5.1	3.4 to 7.6	4
TnT and TnI combined†					
Total death	42/2,088	69/1,068	3.3	2.2 to 4.8	7
Cardiac death	28/1,641	55/792	5.0	3.2 to 7.9	7

*Outcomes of cardiac death and total death are pooled. †Some studies provided both troponin T (TnT) and I (TnI) data. For the combined analysis, data from 1 marker were chosen randomly. Reprinted with permission from Heidenreich PA, Go A, Melsop KA, et al. Prediction of risk for patients with unstable angina. Evidence Report/Technology Assessment No. 31 (prepared by the UCSF-Stanford Evidence-Based Practice Center under contract no. 290-97-0013). AHRQ publication no. 01-E001. Rockville, MD: Agency for Healthcare Research and Quality, December 2000. Available at: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat1.chapter.45627. Accessed August 10, 2006 (232).

ACS = acute coronary syndrome; CI = confidence interval; RR = relative risk; UA = unstable angina.

Troponin elevation has important therapeutic implications. It permits the identification of high-risk patients and of subsets of patients who will benefit from specific therapies. Thus, among patients with UA/NSTEMI, those with elevated cTn benefit from treatment with platelet GP IIb/IIIa inhibitors, whereas those without such elevation may not benefit or may even experience a deleterious effect. For example, in the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) trial, the rates of death or nonfatal MI with cTnT elevation were 23.9% with placebo versus 9.5% with abciximab ($p = 0.002$) (240). Similar results have been reported for cTnI and cTnT with use of tirofiban (241). The benefit of LMWH was also greater in UA/NSTEMI patients with positive cTn. In the Fragmin during Instability in Coronary Artery Disease (FRISC) trial, the rates of death or nonfatal MI through 40 d increased progressively in the placebo group from 5.7% in the lowest tertile to 12.6% and 15.7% in the second and third tertiles, respectively, compared with rates of 4.7%, 5.7%, and 8.9%, respectively, in the dalteparin group, which represents risk reductions in events by increasing tertiles of 17.5%, 43%, and 55% (242). Similar differential benefits were observed with enoxaparin versus unfractionated heparin (UFH) in the ESSENCE trial (169). By contrast and of interest, patients with UA/NSTEMI but without elevated cTnT in the Clopidogrel in Unstable angina to prevent Recurrent ischemic Events (CURE) trial benefited as much from clopidogrel, a platelet P2Y12 adenosine diphosphate (ADP) receptor inhibitor, as patients with elevated levels (243). The placebo-controlled Intracoronary Stenting and Antithrombotic Regimen–Rapid Early Action for Coronary Treatment (ISAR-REACT)-2 trial compared triple-antiplatelet therapy with ASA, clopidogrel, and abciximab to double therapy with ASA and clopidogrel in patients with UA/NSTEMI undergoing PCI; 52% of patients were troponin positive, and 48% were troponin negative. The 30-d event rates were similar at 4.6% in patients with normal cTnT levels but were reduced by close to 30% with the triple therapy (13.1% vs. 18.3%) in patients with elevated levels (244). The reasons for the differential benefit could pertain to a benefit that does not emerge in the low-risk patient, or that is overshadowed by complications related to treatment.

Such also appears to be the case with the GP IIb/IIIa antagonists and with an invasive management strategy that includes application of interventional procedures. Indeed, in 2 trials that compared an early routine invasive strategy to a routine noninvasive strategy, the FRISC-II and Treat Angina with Aggrastat and determine Cost of Therapy with Invasive or Conservative Strategy (TACTICS) TIMI-18 trials, patients who profited from the early invasive treatment strategy were those at high risk as determined by cTnT levels and the admission ECG. In the FRISC study, the invasive strategy reduced the 12-month risk of death or MI by 40% (13.2% vs. 22.1%, $p = 0.001$) in the cohort with both ST depression and a cTnT level of 0.03 mcg per liter or greater, but the absolute gain of the invasive strategy was insignificant in the cohorts with either ST depression, cTnT level elevation, or neither of these findings (245). In the TACTICS TIMI-28 study, subgroups of patients with no ECG changes, a low TIMI score, and no cTn elevation showed no benefit from the invasive strategy, whereas those with positive cTn, independent of the presence of elevated CK-MB levels, showed markedly reduced odds of adverse clinical events of 0.13 at 30 d (95% confidence interval [CI] = 0.04 to 0.39) and 0.29 at 180 d (95% CI = 0.16 to 0.52) (246).

2.2.8.2.1.1. Clinical Use of Marker Change Scores. A newer method to both identify and exclude MI within 6 h of symptoms is to rely on changes in serum marker levels (delta values) over an abbreviated time interval (e.g., 2 h) as opposed to the traditional approach of performing serial measurements over 6 to 8 h (212,214,247–250). Because assays are becoming more sensitive and precise, this method permits the identification of increasing values while they are still in the normal or indeterminate range of the assay. By relying on delta values for the identification or exclusion of MI, higher-risk patients with positive delta values can be selected earlier for more aggressive anti-ischemic therapy (e.g., GP IIb/IIIa inhibitors), and lower-risk patients with negative delta values can be considered for early stress testing (212,214,249–251). One study of 1,042 patients found the addition of a 3-h delta CK-MB to result in a sensitivity of 93% and a specificity of 94% for MI (248). In another study of 2,074 consecutive ED chest pain patients, a 2-h delta CK-MB in conjunction with a 2-h delta troponin I measurement had a sensitivity for acute MI of 93% and specificity of 94% in patients whose initial ECG was nondiagnostic for injury. When combined with physician judgment and selective nuclear stress testing, the sensitivity for MI was 100% with specificity of 82%, and the sensitivity for 30-d ACS was 99.1% with specificity of 87% (214). Because there are no manufacturer-recommended delta cutoff values, the appropriate delta values for identification and exclusion of MI should take into account the sensitivity and precision of the specific assay utilized and should be confirmed by in-house studies. It also is important for delta values to be measured on the same instrument owing to subtle variations in calibration among individual instruments, even of the same model.

Another method to exclude MI within 6 h of symptom onset is the multimarker approach, which utilizes the serial measurement of myoglobin (i.e., a very early marker) in combination with the serial measurements of cTn and/or CK-MB (i.e., a later marker) (252–256). Studies have reported that multimarker measurements at baseline and 90 min have a sensitivity for MI of approximately 95% with a high negative predictive value, thus allowing for the early exclusion of MI when combined with clinical judgment (254,255). However, because of the low specificity of the multimarker strategy (mainly due to the lower specificity of myoglobin), a positive multimarker test is inadequate to

diagnose MI and requires confirmation with a later-appearing definitive marker (254,257).

2.2.8.2.1.2. Bedside Testing for Cardiac Markers. Cardiac markers can be measured in the central chemistry laboratory or with point-of-care instruments in the ED with desktop devices or handheld bedside rapid qualitative assays (229). When a central laboratory is used, results should be available as soon as possible, with a goal of within 60 min. Point-of-care systems, if implemented at the bedside, have the advantage of reducing delays due to transportation and processing in a central laboratory and can eliminate delays due to the lack of availability of central laboratory assays at all hours. Certain portable devices can simultaneously measure myoglobin, CK-MB, and troponin I (249). These advantages of point-of-care systems must be weighed against the need for stringent quality control and appropriate training of ED personnel in assay performance and the higher costs of point-of-care testing devices relative to determinations in the central laboratory. In addition, these point-of-care assays at present are qualitative or, at best, semiquantitative. To date, bedside testing has not succeeded in becoming widely accepted or applied.

2.2.8.3. MYOGLOBIN AND CK-MB SUBFORMS COMPARED WITH TROPONINS

Myoglobin, a low-molecular-weight heme protein found in both cardiac and skeletal muscle, is not cardiac specific, but it is released more rapidly from infarcted myocardium than are CK-MB and cTn and can be detected as early as 2 h after the onset of myocardial necrosis. However, the clinical value of serial determinations of myoglobin for the diagnosis of MI is limited by its brief duration of elevation of less than 24 h. Thus, an isolated early elevation in patients with a nondiagnostic ECG should not be relied on to make the diagnosis of MI but should be supplemented by a more cardiac-specific marker (258). Creatine kinase-MB subforms are also efficient for the early diagnosis of MI and have a similar specificity to that of CK-MB but require special expertise, with no real advantage over better standardized and more easily applied cTn testing.

2.2.8.4. SUMMARY COMPARISON OF BIOMARKERS OF NECROSIS: SINGLY AND IN COMBINATION

Table 10 compares the advantages and disadvantages of cardiac biomarkers of necrosis that are currently used for the evaluation and management of patients with suspected ACS but without ST-segment elevation on the 12-lead ECG. Given the overlapping time frame of the release pattern of cardiac biomarkers, it is important that clinicians incorporate the time from the onset of the patient's symptoms into their assessment of the results of biomarker measurements (11,252,259,260) (Fig. 5).

Many patients with suspected ACS have combined assessments of troponin and CK-MB. When baseline troponin and CK-MB were used together for diagnostic and risk assessment across the spectrum of chest pain syndromes in a large database that consisted of several clinical trials, those with positive results for both markers were at highest short-term (24 h and 30 d) risk of death or MI (261). However, those with baseline troponin elevation without CK-MB elevation also were at increased 30-d risk, whereas risk with isolated CK-MB elevation was lower and not significantly different than if both markers were negative (261).

In summary, the cTns are currently the markers of choice for the diagnosis of MI. They have a sensitivity and specificity as yet unsurpassed, which allows for the recognition of very small amounts of myocardial necrosis. These small areas of infarction are the consequence of severe ischemia and/or distal microembolization of debris from an unstable thrombogenic plaque. The unstable plaques are likely responsible for the high-risk situation. Thus, cTns as biomarkers are not only markers of cell necrosis but also of an active thrombogenic plaque, and hence, they indicate prognosis and are useful in guiding therapies. Although not quite as sensitive or specific as the cTns, CK-MB by mass assay is a second-choice marker that remains useful for the diagnosis of MI extension and of periprocedural MI. Routine use of myoglobin and other markers is not generally recommended.

Because many methods exist, many with multiple test generations, for cardiac biomarker testing in practice and in published reports, physicians should work with their clinical laboratories to ensure use of and familiarity with contemporary test technology, with appropriate, accurate ranges of normal and diagnostic cutoffs, specific to the assay used.

2.2.9. Other Markers and Multimarker Approaches

Besides markers of myocardial necrosis, markers of pathophysiological mechanisms implicated in ACS are under investigation and could become useful to determine pathophysiology, individualize treatment, and evaluate therapeutic effects. In considering the clinical application of new biomarkers, it is important to determine that they provide incremental value over existing biomarkers. A multimarker approach to risk stratification of UA/NSTEMI (e.g., simultaneous assessment of cTnI, C-reactive protein [CRP], and BNP) has been advocated as a potential advance over single biomarker assessment (262,263). Further evaluation of a multimarker approach will be of interest.

2.2.9.1. ISCHEMIA

Other new biochemical markers for the detection of myocardial necrosis are either less useful or have been less well studied than those mentioned above. An example is ischemia-modified albumin found soon after transient coronary occlusion and preceding any significant elevations in myoglobin, CK-MB, or cTnI. This modified albumin depends on a reduced capacity of human albumin to bind exogenous cobalt during ischemia (264,265). Choline is released upon the cleavage of phospholipids and could also serve as a marker of ischemia. Growth-differentiation factor-15 (GDF-15), a member of the transforming growth

Table 10. Biochemical Cardiac Markers for the Evaluation and Management of Patients With Suspected ACS But Without ST-Segment Elevation on 12-Lead ECG

Marker	Advantages	Disadvantages	Point-of-Care Test Available?	Comment	Clinical Recommendation
Cardiac troponins	1. Powerful tool for risk stratification 2. Greater sensitivity and specificity than CK-MB 3. Detection of recent MI up to 2 weeks after onset 4. Useful for selection of therapy 5. Detection of reperfusion	1. Low sensitivity in very early phase of MI (less than 6 h after symptom onset) and requires repeat measurement at 8 to 12 h, if negative 2. Limited ability to detect late minor reinfarction	Yes	Data on diagnostic performance and potential therapeutic implications increasingly available from clinical trials	Useful as a single test to efficiently diagnose NSTEMI (including minor myocardial damage), with serial measurements. Clinicians should familiarize themselves with diagnostic "cutoffs" used in their local hospital laboratory
CK-MB	1. Rapid, cost-efficient, accurate assays 2. Ability to detect early reinfarction	1. Loss of specificity in setting of skeletal muscle disease or injury, including surgery 2. Low sensitivity during very early MI (less than 6 h after symptom onset) or later after symptom onset (more than 36 h) and for minor myocardial damage (detectable with troponins)	Yes	Familiar to majority of clinicians	Prior standard and still acceptable diagnostic test in most clinical circumstances
Myoglobin	1. High sensitivity 2. Useful in early detection of MI 3. Detection of reperfusion 4. Most useful in ruling out MI	1. Very low specificity in setting of skeletal muscle injury or disease 2. Rapid return to normal range limits sensitivity for later presentations	Yes	More convenient early marker than CK-MB isoforms because of greater availability of assays for myoglobin; rapid-release kinetics make myoglobin useful for noninvasive monitoring of reperfusion in patients with established MI	

ACS = acute coronary syndrome; CK-MB = MB fraction of creatine kinase; ECG = electrocardiogram; h = hours; MI = myocardial infarction; NSTEMI = non–ST-elevation MI.

factor-β cytokine superfamily that is induced after ischemia-and-reperfusion injury, is a new biomarker that has been reported to be of incremental prognostic value for death in patients with UA/NSTEMI (265a).

2.2.9.2. COAGULATION

Markers of activity of the coagulation cascade, including elevated plasma levels of fibrinogen, the prothrombin fragments, fibrinopeptide, and D-dimers, are elevated in ACS but have little discriminative ability for a specific pathophysiology, diagnosis, or treatment assessments (266,267). In experimental studies, markers of thrombin generation are blocked by anticoagulants but reactivate after their discontinuation (268) and are not affected by clopidogrel (269).

2.2.9.3. PLATELETS

Platelet activation currently is difficult to assess directly in vivo. New methods, however, are emerging that should allow a better and more efficient appraisal of their state of activation and of drug effects (270–272). Alternative markers of platelet activity are also being studied, including CD40L, platelet-neutrophil coaggregates, P-selectin, and platelet microparticles.

2.2.9.4. INFLAMMATION

Systemic markers of inflammation are being widely studied and show promise for providing additional insights into pathophysiological mechanisms proximal to and triggering thrombosis, as well as suggesting novel therapeutic approaches. White blood cell counts are elevated in patients with MI, and this elevation has prognostic implications. Patients without biochemical evidence of myocardial necrosis but who have elevated CRP levels on admission or past the acute-phase reaction after 1 month and who have values in the highest quartile are at an increased risk of an adverse outcome (273–275). Elevated levels of interleukin-6, which promotes the synthesis of CRP, and of other proinflamma-

tory cytokines also have been studied for their prognostic value (276). Other potentially useful markers are levels of circulating soluble adhesion molecules, such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin (277); the pregnancy–associated plasma protein-A, which is a zinc-binding matrix metalloproteinase released with neorevascularization and believed to be a marker of incipient plaque rupture (278); myeloperoxidase, a leukocyte-derived protein that generates reactive oxidant species that contribute to tissue damage, inflammation, and immune processes within atherosclerotic lesions (279); and others. At this writing, none of these have been adequately studied or validated to be recommended for routine clinical application in UA/NSTEMI.

2.2.9.5. B-TYPE NATRIURETIC PEPTIDES

One newer biomarker of considerable interest that now may be considered in the guidelines recommendations is BNP. B-type natriuretic peptide is a cardiac neurohormone released upon ventricular myocyte stretch as proBNP, which is enzymatically cleaved to the N-terminal proBNP (NT-proBNP) and, subsequently, to BNP. The usefulness of assessing this neurohormone was first shown for the diagnosis and evaluation of HF. Since then, numerous prospective studies and data from large data sets have documented its powerful prognostic value independent of conventional risk factors for mortality in patients with stable and unstable CAD (263,280–284). A review of available studies in ACS showed that when measured at first patient contact or during the hospital stay, the natriuretic peptides are strong predictors of both short- and long-term mortality in patients with STEMI and UA/NSTEMI (280). Increasing levels of NT-proBNP are associated with proportionally higher short- and long-term mortality rates; at 1 year, mortality rates with increasing quartiles were 1.8%, 3.9%, 7.7%, and 19.2%, respectively (p less than 0.001) in the GUSTO-IV trial of 6,809 patients (284). This prognostic value was independent of a previous history of HF and of clinical or laboratory signs of LV dysfunction on admission or during hospital stay (280). B-type natriuretic peptide and NT-proBNP levels can now be measured easily and rapidly in most hospital laboratories.

2.3. Immediate Management

RECOMMENDATIONS

CLASS I

1. **The history, physical examination, 12-lead ECG, and initial cardiac biomarker tests should be integrated to assign patients with chest pain into 1 of 4 categories: a noncardiac diagnosis, chronic stable angina, possible ACS, and definite ACS. *(Level of Evidence: C)***
2. **Patients with probable or possible ACS but whose initial 12-lead ECG and cardiac biomarker levels are normal should be observed in a facility with cardiac monitoring (e.g., chest pain unit or hospital telemetry ward), and repeat ECG (or continuous 12-lead ECG monitoring) and repeat cardiac biomarker measurement(s) should be obtained at predetermined, specified time intervals (see Section 2.2.8). *(Level of Evidence: B)***
3. **In patients with suspected ACS in whom ischemic heart disease is present or suspected, if the follow-up 12-lead ECG and cardiac biomarkers measurements are normal, a stress test (exercise or pharmacological) to provoke ischemia should be performed in the ED, in a chest pain unit, or on an outpatient basis in a timely fashion (within 72 h) as an alternative to inpatient admission. Low-risk patients with a negative diagnostic test can be managed as outpatients. *(Level of Evidence: C)***
4. **In low-risk patients who are referred for outpatient stress testing (see above), precautionary appropriate pharmacotherapy (e.g., ASA, sublingual NTG, and/or beta blockers) should be given while awaiting results of the stress test. *(Level of Evidence: C)***
5. **Patients with definite ACS and ongoing ischemic symptoms, positive cardiac biomarkers, new ST-segment deviations, new deep T-wave inversions, hemodynamic abnormalities, or a positive stress test should be admitted to the hospital for further management. Admission to the critical care unit is recommended for those with active, ongoing ischemia/injury or hemodynamic or electrical instability. Otherwise, a telemetry step-down unit is reasonable. *(Level of Evidence: C)***
6. **Patients with possible ACS and negative cardiac biomarkers who are unable to exercise or who have an abnormal resting ECG should undergo a pharmacological stress test. *(Level of Evidence: B)***
7. **Patients with definite ACS and ST-segment elevation in leads V_7 to V_9 due to left circumflex occlusion should be evaluated for immediate reperfusion therapy. *(Level of Evidence: A)***
8. **Patients discharged from the ED or chest pain unit should be given specific instructions for activity, medications, additional testing, and follow-up with a personal physician. *(Level of Evidence: C)***

CLASS IIa

In patients with suspected ACS with a low or intermediate probability of CAD, in whom the follow-up 12-lead ECG and cardiac biomarkers measurements are normal, performance of a noninvasive coronary imaging test (i.e., CCTA) is reasonable as an alternative to stress testing. *(Level of Evidence: B)*

By integrating information from the history, physical examination, 12-lead ECG, and initial cardiac biomarker tests, clinicians can assign patients to 1 of 4 categories: noncardiac diagnosis, chronic stable angina, possible ACS, and definite ACS (Fig. 2).

Patients who arrive at a medical facility in a pain-free state, have unchanged or normal ECGs, are hemodynamically stable, and do not have elevated cardiac biomarkers represent more of a diagnostic than an urgent therapeutic challenge. Evaluation begins in these patients by obtaining information from the history, physical examination, and ECG (Tables 6 and 7) to be used to confirm or reject the diagnosis of UA/NSTEMI.

Patients with a low likelihood of CAD should be evaluated for other causes of the noncardiac presentation, including musculoskeletal pain; gastrointestinal disorders, such as esophageal spasm, gastritis, peptic ulcer disease, or cholecystitis; intrathoracic disease, such as musculoskeletal discomfort, pneumonia, pleurisy, pneumothorax, pulmonary

embolus, dissecting aortic aneurysm, myocarditis, or pericarditis; and neuropsychiatric disease, such as hyperventilation or panic disorder (Fig. 2, B1). Patients who are found to have evidence of 1 of these alternative diagnoses should be excluded from management with these guidelines and referred for appropriate follow-up care (Fig. 2, C1). Reassurance should be balanced with instructions to return for further evaluation if symptoms worsen or if the patient fails to respond to symptomatic treatment. Chronic stable angina may also be diagnosed in this setting (Fig. 2, B2), and patients with this diagnosis should be managed according to the ACC/AHA 2002 Guideline Update for the Management of Patients With Chronic Stable Angina (4).

Patients with possible ACS (Fig. 2, B3 and D1) are candidates for additional observation in a specialized facility (e.g., chest pain unit) (Fig. 2, E1). Patients with definite ACS (Fig. 2, B4) are triaged on the basis of the pattern of the 12-lead ECG. Patients with ST-segment elevation (Fig. 2, C3) are evaluated for immediate reperfusion therapy (Fig. 2, D3) and managed according to the ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (1), whereas those without ST-segment elevation (Fig. 2, C2) are either managed by additional observation (Fig. 2, E1) or admitted to the hospital (Fig. 2, H3). Patients with low-risk ACS (Table 6) without transient ST-segment depressions greater than or equal to 0.05 mV (0.5 mm) or T-wave inversions greater than or equal to 0.2 mV (2 mm), without positive cardiac biomarkers, and with a negative stress test or CCTA (Fig. 2, H1) may be discharged and treated as outpatients (Fig. 2, I1). Low-risk patients may have a stress test within 3 d of discharge.

2.3.1. Chest Pain Units

To facilitate a more definitive evaluation while avoiding the unnecessary hospital admission of patients with possible ACS (Fig. 2, B3) and low-risk ACS (Fig. 2, F1), as well as the inappropriate discharge of patients with active myocardial ischemia without ST-segment elevation (Fig. 2, C2), special units have been established that are variously referred to as "chest pain units" and "short-stay ED coronary care units." Personnel in these units use critical pathways or protocols designed to arrive at a decision about the presence or absence of myocardial ischemia and, if present, to characterize it further as UA or NSTEMI and to define the optimal next step in the care of the patient (e.g., admission, acute intervention) (87,214,285,286). The goal is to arrive at such a decision after a finite amount of time, which usually is between 6 and 12 h but may extend up to 24 h depending on the policies in individual hospitals. Typically, the patient undergoes a predetermined observation period with serial cardiac biomarkers and ECGs. At the end of the observation period, the patient is reevaluated and then generally undergoes functional cardiac testing (e.g., resting nuclear scan or echocardiography) and/or stress testing (e.g., treadmill, stress echocardiography, or stress nuclear testing) or noninvasive coronary imaging study (i.e., CCTA) (see Section 2.3.2). Those patients who have a recurrence of chest pain strongly suggestive of ACS, a positive biomarker value, a significant ECG change, or a positive functional/stress test or CCTA are generally admitted for inpatient evaluation and treatment. Although chest pain units are useful, other appropriate observation areas in which patients with chest pain can be evaluated may be used as well, such as a section of the hospital's cardiac telemetry ward.

The physical location of the chest pain unit or the site where patients with chest pain are observed is variable, ranging from a specifically designated area of the ED to a separate hospital unit with the appropriate equipment to observational status (24-h admission) on a regular hospital telemetry ward (287). Similarly, the chest pain unit may be administratively a part of the ED and staffed by emergency physicians or may be administered and staffed separately or as part of the hospital cardiovascular service. Capability of chest pain units generally includes continuous monitoring of the patient's ECG, ready availability of cardiac resuscitation equipment and medications, and appropriate staffing with nurses and physicians. The ACEP has published guidelines that recommend a program for the continuous monitoring of outcomes of patients evaluated in such units and the impact on hospital resources (288). A consensus panel statement from ACEP emphasized that chest pain units should be considered as part of a multifaceted program that includes efforts to minimize patient delays in seeking medical care and delays in the ED itself (288).

It has been reported, both from studies with historical controls and from randomized trials, that the use of chest pain units is cost-saving compared with an in-hospital evaluation to "rule out MI" (289,290). The potential cost savings of a chest pain unit varies depending on the practice pattern for the disposition of chest pain patients at individual hospitals (289). Hospitals with a high admission rate of low-risk patients to rule out MI (70% to 80%) will experience the largest cost savings by implementing a chest pain unit approach but will have the smallest impact on the number of missed MI patients. In contrast, hospitals with relatively low admission rates of such patients (30% to 40%) will experience greater improvements in the quality of care because fewer MI patients will be missed but will experience a smaller impact on costs because of the low baseline admission rate.

Farkouh et al. (102) extended the use of a chest pain unit in a separate portion of the ED to include patients at an intermediate risk of adverse clinical outcome on the basis of the previously published Agency for Healthcare Research and Quality guidelines for the management of UA (124) (Table 7). They reported a 46% reduction in the ultimate need for hospital admission in intermediate-risk patients after a median stay of 9.2 h in the chest pain unit. Extension of the use of chest pain units to intermediate-risk patients in an effort to reduce inpatient costs is facilitated by making available diagnostic testing modalities such as treadmill

testing and stress imaging (echocardiographic, nuclear, or magnetic resonance) or CCTA 7 d a week (291).

Patients with chest discomfort for whom a specific diagnosis cannot be made after a review of the history, physical examination, initial 12-lead ECG, and cardiac biomarker data should undergo a more definitive evaluation. Several categories of patients should be considered according to the algorithm shown in Figure 2:

- Patients with possible ACS (Fig. 2, B3) are those who had a recent episode of chest discomfort at rest not entirely typical of ischemia but who are pain free when initially evaluated, have a normal or unchanged ECG, and have no elevations of cardiac biomarkers.
- Patients with a recent episode of typical ischemic discomfort that either is of new onset or is severe or that exhibits an accelerating pattern of previous stable angina (especially if it has occurred at rest or is within 2 weeks of a previously documented MI) should initially be considered to have a "definite ACS" (Fig. 2, B4). However, such patients may be at a low risk if their ECG obtained at presentation has no diagnostic abnormalities and the initial serum cardiac biomarkers (especially cardiac-specific troponins) are normal (Fig. 2, C2 and D1). As indicated in the algorithm, patients with either "possible ACS" (Fig. 2, B3) or "definite ACS" (Fig. 2, B4) but with nondiagnostic ECGs and normal initial cardiac markers (Fig. 2, D1) are candidates for additional observation in the ED or in a specialized area such as a chest pain unit (Fig. 2, E1). In contrast, patients who present without ST-segment elevation but who have features indicative of active ischemia (ongoing pain, ST-segment and/or T-wave changes, positive cardiac biomarkers, or hemodynamic instability; Fig. 2, D2) should be admitted to the hospital (Fig. 2, H3).

2.3.2. Discharge From ED or Chest Pain Unit

The initial assessment of whether a patient has UA/NSTEMI and which triage option is most suitable generally should be made immediately on the patient's arrival at a medical facility. Rapid assessment of a patient's candidacy for additional observation can be accomplished based on the status of the symptoms, ECG findings, and initial serum cardiac biomarker measurement.

Patients who experience recurrent ischemic discomfort, evolve abnormalities on a follow-up 12-lead ECG or on cardiac biomarker measurements, or develop hemodynamic abnormalities such as new or worsening HF (Fig. 2, D2) should be admitted to the hospital (Fig. 2, H3) and managed as described in Section 3.

Patients who are pain free, have either a normal or nondiagnostic ECG or one that is unchanged from previous tracings, and have a normal set of initial cardiac biomarker measurements are candidates for further evaluation to screen for nonischemic discomfort (Fig. 2, B1) versus a low-risk ACS (Fig. 2, D1). If the patient is low risk (Table 7) and does not experience any further ischemic discomfort and a follow-up 12-lead ECG and cardiac biomarker measurements after 6 to 8 h of observation are normal (Fig. 2, F1), the patient may be considered for an early stress test to provoke ischemia or CCTA to assess for obstructive CAD (Fig. 2, G1). This test can be performed before the discharge and should be supervised by an experienced physician. Alternatively, the patient may be discharged and return for stress testing as an outpatient within 72 h. The exact nature of the test may vary depending on the patient's ability to exercise on either a treadmill or bicycle and the local expertise in a given hospital setting (e.g., availability of different testing modalities at different times of the day or different days of the week) (292). Patients who are capable of exercise and who are free of confounding features on the baseline ECG, such as bundle-branch block, LV hypertrophy, or paced rhythms, can be evaluated with routine symptom-limited conventional exercise stress testing. Patients who are incapable of exercise or who have an uninterpretable baseline ECG should be considered for pharmacological stress testing with either nuclear perfusion imaging or 2-dimensional echocardiography, or magnetic resonance (175,293,294). Alternatively, it is reasonable to perform a non-invasive coronary imaging test (i.e., CCTA). An imaging-enhanced test also may be more predictive in women than conventional ECG exercise stress testing (see Section 6.1.).

Two imaging modalities, CMR and multidetector computed tomography for coronary calcification and CCTA, are increasingly becoming clinically validated and applied and hold promise as alternative or supplementary imaging modalities for assessing patients who present with chest pain syndromes (25,294,295). Cardiac magnetic resonance has the capability of assessing cardiac function, perfusion, and viability in the same setting. Its advantages are excellent resolution (approximately 1 mm) of cardiac structures and avoidance of exposure to radiation and iodinated contrast. Disadvantages include long study time, confined space (claustrophobia), and (current) contraindication to the presence of pacemakers/defibrillators. To evaluate for ischemic heart disease, an adenosine first-pass gadolinium perfusion study is combined with assessment of regional and global function and viability (gadolinium delayed study). Direct coronary artery imaging is better assessed by CCTA (see below). One study indicated a sensitivity of 89% and specificity of 87% for combined adenosine stress and gadolinium delayed enhancement (viability) CMR testing for CAD (296). Dobutamine CMR stress testing can be used as an alternative to adenosine perfusion CMR (e.g., in asthmatic patients).

Coronary CT angiography with current multidetector technology (i.e., 64 slices beginning in 2005) has been reported to give 90% to 95% or greater sensitivity and specificity for occlusive CAD in early clinical trial experience (297–299). For evaluation of potential UA/NSTEMI, coronary artery calcium scoring followed by CCTA is

typically done in the same sitting. The advantages of CCTA are good to excellent resolution (approximately 0.6 mm) of coronary artery anatomy and short study time (single breath hold). Disadvantages are radiation dose (8 to 24 mSv), contrast dye exposure, and necessity to achieve a slow, regular heart rate (beta blockers are usually required). A lack of large controlled comparative trials and reimbursement issues are current limitations to these technologies. In summary, the high negative predictive value of CCTA is its greatest advantage: if no evidence of either calcified or noncalcified (soft/fibrous) plaque is found, then it is highly unlikely that the patient's symptoms are due to UA/NSTEMI of an atherosclerotic origin. (Note that primary [micro]vascular dysfunction causes of chest pain are not excluded.) In contrast, the positive predictive value of CCTA in determining whether a given plaque or stenosis is causing the signs and symptoms of possible UA/NSTEMI is less clear because although it gives valuable anatomic information, it does not provide functional or physiological assessment. Coronary CT angiography has been judged to be useful for evaluation of obstructive CAD in symptomatic patients (Class IIa, Level of Evidence: B) (25) and appropriate for acute chest pain evaluation for those with intermediate and possibly low pretest probability of CAD when serial ECG and biomarkers are negative (294). It may be particularly appropriate for those with acute chest pain syndromes with intermediate pretest probability of CAD in the setting of nondiagnostic ECG and negative cardiac biomarkers (294).

Because LV function is so integrally related to prognosis and greatly affects therapeutic options, strong consideration should be given to the assessment of LV function with echocardiography or another modality (i.e., CMR, radionuclide, CCTA, or contrast angiography) in patients with documented ischemia. In sites at which stress tests are not available, low-risk patients may be discharged and referred for outpatient stress testing in a timely fashion. Prescription of precautionary anti-ischemic treatment (e.g., ASA, sublingual NTG, and beta blockers) should be considered in these patients while awaiting results of stress testing. Specific instructions also should be given on whether or not to take these medications (e.g., beta blockers) before testing, which may vary depending on the test ordered and patient-specific factors. These patients also should be given specific instructions on what to do and how to seek emergency care for recurrence or worsening of symptoms while awaiting the stress test.

Patients who develop recurrent symptoms during observation suggestive of ACS or in whom the follow-up studies (12-lead ECG, cardiac biomarkers) show new abnormalities (Fig. 2, F2) should be admitted to the hospital (Fig. 2, H3). Patients in whom ACS has been excluded should be reassessed for need for further evaluation of other potentially serious medical conditions that may mimic ACS symptomatology (e.g., pulmonary embolism and aortic dissection).

Because continuity of care is important in the overall management of patients with a chest pain syndrome, the patient's primary physician (if not involved in the care of the patient during the initial episode) should be notified of the results of the evaluation and should receive a copy of the relevant test results. Patients with a noncardiac diagnosis and those with low risk or possible ACS with a negative stress test should be counseled to make an appointment with their primary care physician as outpatients for further investigation into the cause of their symptoms (Fig. 2, I1). They should be seen by a physician as soon after discharge from the ED or chest pain unit as practical and appropriate, that is, usually within 72 h.

Patients with possible ACS (Fig. 5, B3) and those with a definite ACS but a nondiagnostic ECG and normal cardiac biomarkers when they are initially seen (Fig. 2, D1) at institutions without a chest pain unit (or equivalent facility) should be admitted to an inpatient unit. The inpatient unit to which such patients are to be admitted should have the same provisions for continuous ECG monitoring, availability of resuscitation equipment, and staffing arrangements as described above for the design of chest pain units.

3. Early Hospital Care

Patients with UA/NSTEMI, recurrent symptoms suggestive of ACS and/or ECG ST-segment deviations, or positive cardiac biomarkers who are stable hemodynamically should be admitted to an inpatient unit for bed rest with continuous rhythm monitoring and careful observation for recurrent ischemia (a step-down unit) and managed with either an invasive or conservative strategy (Table 11). Patients with continuing discomfort and/or hemodynamic

Table 11. Selection of Initial Treatment Strategy: Invasive Versus Conservative Strategy

Preferred Strategy	Patient Characteristics
Invasive	Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy
	Elevated cardiac biomarkers (TnT or TnI)
	New or presumably new ST-segment depression
	Signs or symptoms of HF or new or worsening mitral regurgitation
	High-risk findings from noninvasive testing
	Hemodynamic instability
	Sustained ventricular tachycardia
	PCI within 6 months
	Prior CABG
	High risk score (e.g., TIMI, GRACE)
	Reduced left ventricular function (LVEF less than 40%)
Conservative	Low risk score (e.g., TIMI, GRACE)
	Patient or physician preference in the absence of high-risk features

CABG = coronary artery bypass graft surgery; GRACE = Global Registry of Acute Coronary Events; HF = heart failure; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction; TnI = troponin I; TnT = troponin T.

instability should be hospitalized for at least 24 h in a coronary care unit characterized by a nursing-to-patient ratio sufficient to provide 1) continuous rhythm monitoring, 2) frequent assessment of vital signs and mental status, 3) documented ability to perform defibrillation quickly after the onset of ventricular fibrillation, and 4) adequate staff to perform these functions. Patients should be maintained at that level of care until they have been observed for an adequate period of time, generally at least 24 h, without any of the following major complications: sustained ventricular tachycardia or fibrillation, sinus tachycardia, high-degree atrioventricular (AV) block, sustained hypotension, recurrent ischemia documented by symptoms or ST-segment change, new mechanical defect (ventricular septal defect or mitral regurgitation), or HF. Shorter periods of monitoring might be appropriate for selected patients who are successfully reperfused and who have normal LV function and minimal or no necrosis.

Once a patient with documented high-risk ACS is admitted, standard medical therapy is indicated as discussed later. Unless a contraindication exists, these patients generally should be treated with ASA, a beta blocker, anticoagulant therapy, a GP IIb/IIIa inhibitor, and a thienopyridine (i.e., clopidogrel; initiation may be deferred until a revascularization decision is made). Critical decisions are required regarding the angiographic (invasive) strategy. One option is a routine angiographic approach in which coronary angiography and revascularization are performed unless a contraindication exists. Within this approach, a common past strategy has called for a period of medical stabilization. Increasingly, physicians are taking a more aggressive approach, with coronary angiography and revascularization performed within 24 h of admission; the rationale for the more aggressive approach is the protective effect of carefully administered anticoagulant and antiplatelet therapy on procedural outcome. The alternative approach, commonly referred to as the "initial conservative strategy" (see Section 3.3), is guided by ischemia, with angiography reserved for patients with recurrent ischemia or a high-risk stress test despite medical therapy. Regardless of the angiographic strategy, an assessment of LV function is recommended in patients with documented ischemia because of the imperative to treat patients who have impaired LV function with ACE inhibitors, beta blockers, and, when HF or diabetes mellitus is present, aldosterone antagonists; when the coronary anatomy is appropriate (e.g., 3-vessel coronary disease), CABG is appropriate (see Section 4). When the coronary angiogram is obtained, a left ventriculogram may be obtained at the same time. When coronary angiography is not scheduled, echocardiography, nuclear ventriculography, or magnetic resonance imaging or CT angiography can be used to evaluate LV function.

3.1. Anti-Ischemic and Analgesic Therapy

RECOMMENDATIONS FOR ANTI-ISCHEMIC THERAPY

CLASS I

1. Bed/chair rest with continuous ECG monitoring is recommended for all UA/NSTEMI patients during the early hospital phase. *(Level of Evidence: C)*
2. Supplemental oxygen should be administered to patients with UA/NSTEMI with an arterial saturation less than 90%, respiratory distress, or other high-risk features for hypoxemia. (Pulse oximetry is useful for continuous measurement of SaO_2.) *(Level of Evidence: B)*
3. Patients with UA/NSTEMI with ongoing ischemic discomfort should receive sublingual NTG (0.4 mg) every 5 min for a total of 3 doses, after which assessment should be made about the need for intravenous NTG, if not contraindicated. *(Level of Evidence: C)*
4. Intravenous NTG is indicated in the first 48 h after UA/NSTEMI for treatment of persistent ischemia, HF, or hypertension. The decision to administer intravenous NTG and the dose used should not preclude therapy with other proven mortality-reducing interventions such as beta blockers or ACE inhibitors. *(Level of Evidence: B)*
5. Oral beta-blocker therapy should be initiated within the first 24 h for patients who do not have 1 or more of the following: 1) signs of HF, 2) evidence of a low-output state, 3) increased risk* for cardiogenic shock, or 4) other relative contraindications to beta blockade (PR interval greater than 0.24 s, second or third degree heart block, active asthma, or reactive airway disease). *(Level of Evidence: B)*
6. In UA/NSTEMI patients with continuing or frequently recurring ischemia and in whom beta blockers are contraindicated, a nondihydropyridine calcium channel blocker (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of clinically significant LV dysfunction or other contraindications. *(Level of Evidence: B)*
7. An ACE inhibitor should be administered orally within the first 24 h to UA/NSTEMI patients with pulmonary congestion or LV ejection fraction (LVEF) less than or equal to 0.40, in the absence of hypotension (systolic blood pressure less than 100 mm Hg or less than 30 mm Hg below baseline) or known contraindications to that class of medications. *(Level of Evidence: A)*
8. An angiotensin receptor blocker should be administered to UA/NSTEMI patients who are intolerant of ACE inhibitors and have either clinical or radiological signs of HF or LVEF less than or equal to 0.40. *(Level of Evidence: A)*
9. Because of the increased risks of mortality, reinfarction, hypertension, HF, and myocardial rupture associated with their use, nonsteroidal anti-inflammatory drugs (NSAIDs), except for ASA, whether nonselective or cyclooxygenase (COX)-2–selective agents, should be discontinued at the time a patient presents with UA/NSTEMI. *(Level of Evidence: C)*

*Risk factors for cardiogenic shock (the greater the number of risk factors present, the higher the risk of developing cardiogenic shock): age greater than 70 years, systolic blood pressure less than 120 mmHg, sinus tachycardia greater than 110 or heart rate less than 60, increased time since onset of symptoms of UA/NSTEMI.

CLASS IIa

1. It is reasonable to administer supplemental oxygen to all patients with UA/NSTEMI during the first 6 h after presentation. *(Level of Evidence: C)*
2. In the absence of contradictions to its use, it is reasonable to administer morphine sulfate intravenously to UA/NSTEMI patients if there is uncontrolled ischemic chest discomfort despite NTG, provided that additional therapy is used to manage the underlying ischemia. *(Level of Evidence: B)*
3. It is reasonable to administer intravenous (IV) beta blockers at the time of presentation for hypertension to UA/NSTEMI patients who do not have 1 or more of the following: 1) signs of HF, 2) evidence of a low-output state, 3) increased risk* for cardiogenic shock, or 4) other relative contraindications to beta blockade (PR interval greater than 0.24 s, second or third degree heart block, active asthma, or reactive airway disease). *(Level of Evidence: B)*
4. Oral long-acting nondihydropyridine calcium channel blockers are reasonable for use in UA/NSTEMI patients for recurrent ischemia in the absence of contraindications after beta blockers and nitrates have been fully used. *(Level of Evidence: C)*
5. An ACE inhibitor administered orally within the first 24 h of UA/NSTEMI can be useful in patients without pulmonary congestion or LVEF less than or equal to 0.40 in the absence of hypotension (systolic blood pressure less than 100 mm Hg or less than 30 mm Hg below baseline) or known contraindications to that class of medications. *(Level of Evidence: B)*
6. Intra-aortic balloon pump (IABP) counterpulsation is reasonable in UA/NSTEMI patients for severe ischemia that is continuing or recurs frequently despite intensive medical therapy, for hemodynamic instability in patients before or after coronary angiography, and for mechanical complications of MI. *(Level of Evidence: C)*

CLASS IIb

1. The use of extended-release forms of nondihydropyridine calcium channel blockers instead of a beta blocker may be considered in patients with UA/NSTEMI. *(Level of Evidence: B)*
2. Immediate-release dihydropyridine calcium channel blockers in the presence of adequate beta blockade may be considered in patients with UA/NSTEMI with ongoing ischemic symptoms or hypertension. *(Level of Evidence: B)*

CLASS III

1. Nitrates should not be administered to UA/NSTEMI patients with systolic blood pressure less than 90 mm Hg or greater than or equal to 30 mm Hg below baseline, severe bradycardia (less than 50 beats per minute), tachycardia (more than 100 beats per minute) in the absence of symptomatic HF, or right ventricular infarction. *(Level of Evidence: C)*
2. Nitroglycerin or other nitrates should not be administered to patients with UA/NSTEMI who had received a phosphodiesterase inhibitor for erectile dysfunction within 24 h of sildenafil or 48 h of tadalafil use. The suitable time for the administration of nitrates after vardenafil has not been determined. *(Level of Evidence: C)*
3. Immediate-release dihydropyridine calcium channel blockers should not be administered to patients with UA/NSTEMI in the absence of a beta blocker. *(Level of Evidence: A)*

*Risk factors for cardiogenic shock (the greater the number of risk factors present, the higher the risk of developing cardiogenic shock): age greater than 70 years, systolic blood pressure less than 120 mmHg, sinus tachycardia greater than 110 or heart rate less than 60, increased time since onset of symptoms of UA/NSTEMI.

Table 12. Class I Recommendations for Anti-Ischemic Therapy: Continuing Ischemia/Other Clinical High-Risk Features Present*

Bed/chair rest with continuous ECG monitoring
Supplemental oxygen with an arterial saturation less than 90%, respiratory distress, or other high-risk features for hypoxemia. Pulse oximetry can be useful for continuous measurement of SaO_2.
NTG 0.4 mg sublingually every 5 min for a total of 3 doses; afterward, assess need for IV NTG
NTG IV for first 48 h after UA/NSTEMI for treatment of persistent ischemia, HF, or hypertension
Decision to administer NTG IV and dose should not preclude therapy with other mortality-reducing interventions such as beta blockers or ACE inhibitors
Beta blockers (via oral route) within 24 h without a contraindication (e.g., HF) irrespective of concomitant performance of PCI
When beta blockers are contraindicated, a nondihydropyridine calcium channel blocker (e.g., verapamil or diltiazem) should be given as initial therapy in the absence of severe LV dysfunction or other contraindications
ACE inhibitor (via oral route) within first 24 h with pulmonary congestion, or LVEF less than or equal to 0.40, in the absence of hypotension (systolic blood pressure less than 100 mm Hg or less than 30 mm Hg below baseline) or known contraindications to that class of medications
ARB should be administered to UA/NSTEMI patients who are intolerant of ACE inhibitors and have either clinical or radiological signs of heart failure or LVEF less than or equal to 0.40.

*Recurrent angina and/or ischemia-related ECG changes (0.05 mV or greater ST-segment depression or bundle-branch block) at rest or with low-level activity; *or* ischemia associated with HF symptoms, S_3 gallop, or new or worsening mitral regurgitation; *or* hemodynamic instability or depressed LV function (LVEF less than 0.40 on noninvasive study); *or* serious ventricular arrhythmia.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HF = heart failure; IV = intravenous; LV = left ventricular; LVEF = left ventricular ejection fraction; NTG = nitroglycerin; MI = myocardial infarction; PCI = percutaneous coronary intervention; UA/NSTEMI = unstable angina/non–ST-elevation myocardial infarction.

4. An intravenous ACE inhibitor should not be given to patients within the first 24 h of UA/NSTEMI because of the increased risk of hypotension. (A possible exception may be patients with refractory hypertension.) *(Level of Evidence: B)*
5. It may be harmful to administer intravenous beta blockers to UA/NSTEMI patients who have contraindications to beta blockade, signs of HF or low-output state, or other risk factors* for cardiogenic shock. *(Level of Evidence: A)*
6. Nonsteroidal anti-inflammatory drugs (except for ASA), whether nonselective or COX-2–selective agents, should not be administered during hospitalization for UA/NSTEMI because of the increased risks of mortality, reinfarction, hypertension, HF, and myocardial rupture associated with their use. *(Level of Evidence: C)*

The optimal management of UA/NSTEMI has the twin goals of the immediate relief of ischemia and the prevention of serious adverse outcomes (i.e., death or myocardial [re]infarction). This is best accomplished with an approach that includes anti-ischemic therapy (Table 12), antithrombotic therapy (Table 13), ongoing risk stratification, and the use of invasive procedures. Patients who are at intermediate or high risk for adverse outcomes, including those with ongoing ischemia refractory to initial medical therapy and those with evidence of hemodynamic instability, should be admitted whenever possible to a critical care environment with ready access

Table 13. Dosing Table for Antiplatelet and Anticoagulant Therapy in Patients With UA/NSTEMI

Drug*	Initial Medical Treatment	During PCI		After PCI	At Hospital Discharge
		Patient Received Initial Medical Treatment	Patient Did Not Receive Initial Medical Treatment		
Oral Antiplatelet Therapy					
Aspirin	162 to 325 mg nonenteric formulation, orally or chewed	No additional treatment	162 to 325 mg nonenteric formulation orally or chewed	162 to 325 mg daily should be given† for at least 1 month after BMS implantation, 3 months after SES implantation, and 6 months after PES implantation, after which daily chronic aspirin should be continued indefinitely at a dose of 75 to 162 mg	162 to 325 mg daily should be given† for at least 1 month after BMS implantation, 3 months after SES implantation, and 6 months after PES implantation, after which daily chronic aspirin should be continued indefinitely at a dose of 75 to 162 mg
Clopidogrel	LD of 300 to 600 mg orally MD of 75 mg orally per day	A second LD of 300 mg orally may be given to supplement a prior LD of 300 mg	LD of 300 to 600 mg orally	For BMS: 75 mg daily for at least 1 month and ideally up to 1 year. For DES, 75 mg daily for at least 1 year (in patients who are not at high risk of bleeding) (See Fig. 11)	For BMS: 75 mg daily for at least 1 month and ideally up to 1 year. For DES, 75 mg daily for at least 1 year (in patients who are not at high risk of bleeding) (See Fig. 11)
Ticlopidine	LD of 500 mg orally MD of 250 mg orally twice daily	No additional treatment	LD of 500 mg orally	MD of 250 mg orally twice daily (duration same as clopidogrel)	MD of 250 mg orally twice daily (duration same as clopidogrel)
Anticoagulants					
Bivalirudin	0.1 mg per kg bolus, 0.25 mg per kg per h infusion	0.5 mg per kg bolus, increase infusion to 1.75 mg per kg per h	0.75 mg per kg bolus, 1.75 mg per kg per h infusion	No additional treatment or continue infusion for up to 4 h	
Dalteparin	120 IU per kg SC every 12 h (maximum 10,000 IU twice daily)‡	IV GP IIb/IIIa planned: target ACT 200 s using UFH No IV GP IIb/IIIa planned: target ACT 250 to 300 s for HemoTec; 300 to 350 s for Hemochron using UFH	IV GP IIb/IIIa planned: 60 to 70 U per kg§ of UFH No IV GP IIb/IIIa planned: 100 to 140 U per kg of UFH	No additional treatment	
Enoxaparin	LD of 30 mg IV bolus may be given‖ MD = 1 mg per kg SC every 12 h‖; extend dosing interval to 1 mg per kg every 24 h if estimated creatinine clearance less than 30 mL per min‖	Last SC dose less than 8 h: no additional therapy Last SC dose greater than 8 h: 0.3 mg per kg IV bolus	0.5 to 0.75 mg per kg IV bolus	No additional treatment	
Fondaparinux	2.5 mg SC once daily. Avoid for creatinine clearance less than 30 mL per min‖	50 to 60 U per kg IV bolus of UFH is recommended by the OASIS 5 Investigators¶	50 to 60 U per kg IV bolus of UFH is recommended by the OASIS 5 Investigators¶	No additional treatment	
Unfractionated heparin	LD of 60 U per kg (max 4,000 U) as IV bolus‖ MD of IV infusion of 12 U per kg per h (max 1,000 U per h) to maintain aPTT at 1.5 to 2.0 times control (approximately 50 to 70 s)‖	IV GP IIb/IIIa planned: target ACT 200 s No IV GP IIb/IIIa planned: target ACT 250 to 300 s for HemoTec; 300 to 350 s for Hemochron	IV GP IIb/IIIa planned: 60 to 70 U per kg§ No IV GP IIb/IIIa planned: 100 to 140 U per kg	No additional treatment	

Continued on next page

Table 13. Continued

Drug*	Initial Medical Treatment	During PCI		After PCI	At Hospital Discharge
		Patient Received Initial Medical Treatment	Patient Did Not Receive Initial Medical Treatment		
Intravenous Antiplatelet Therapy					
Abciximab	Not applicable	Not applicable	LD of 0.25 mg per kg IV bolus MD of 0.125 mcg per kg per min (max 10 mcg per min)	Continue MD infusion for 12 h	
Eptifibatide	LD of IV bolus of 180 mcg per kg MD of IV infusion of 2.0 mcg per kg per min; reduce infusion by 50% in patients with estimated creatinine clearance less than 50 mL per min	Continue infusion	LD of IV bolus of 180 mcg per kg followed 10 min later by second IV bolus of 180 mcg per kg MD of 2.0 mcg per kg per min; reduce infusion by 50% in patients with estimated creatinine clearance less than 50 mL per min	Continue MD infusion for 18 to 24 h	
Tirofiban	LD of IV infusion of 0.4 mcg per kg per min for 30 min MD of IV infusion of 0.1 mcg per kg per min; reduce rate of infusion by 50% in patients with estimated creatinine clearance less than 30 mL per min	Continue infusion	LD of IV infusion of 0.4 mcg per kg per min for 30 min MD of IV infusion of 0.1 mcg per kg per min; reduce rate of infusion by 50% in patients with estimated creatinine clearance less than 30 mL per min	Continue MD infusion for 18 to 24 h	

Additional considerations include the possibility that a conservatively managed patient may develop a need for PCI, in which case an intravenous bolus of 50 to 60 U per kg of UFH is recommended if fondaparinux was given for initial medical treatment; the safety of this drug combination is not well established. For conservatively managed patients in whom enoxaparin was the initial medical treatment, as noted in the table, additional intravenous enoxaparin is an acceptable option. *This list is in alphabetical order and is not meant to indicate a particular therapy preference. †In patients in whom the physician is concerned about the risk of bleeding, a lower initial ASA dose after PCI of 75 to 162 mg/d is reasonable (Class IIa, LOE: C). ‡Dalteparin was evaluated for management of patients with UA/NSTEMI in an era before the widespread use of important therapies such as stents, clopidogrel, and GP IIb/IIIa inhibitors. Its relative efficacy and safety in the contemporary management era is not well established. §Some operators use less than 60 U per kg of UFH with GP IIb/IIIa blockade, although no clinical trial data exist to demonstrate the efficacy of doses below 60 U per kg in this setting. ‖For patients managed by an initial conservative strategy, agents such as enoxaparin and fondaparinux offer the convenience advantage of SC administration compared with an intravenous infusion of UFH. They are also less likely to provoke heparin-induced thrombocytopenia than UFH. Available data suggest fondaparinux is associated with less bleeding than enoxaparin in conservatively managed patients using the regimens listed. ¶Personal communication, OASIS 5 Investigators, July 7, 2006. Note that this regimen has not been rigorously tested in prospective randomized trials.

ACT = activated clotting time; BMS = bare-metal stent; GP = glycoprotein; h = hour; IU = international unit; IV = intravenous; LD = loading dose; MD = maintenance dose; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent; SC = subcutaneous; SES = sirolimus-eluting stent; U = units; UA/NSTEMI = unstable angina/non–ST-elevation myocardial infarction; UFH = unfractionated heparin.

to invasive cardiovascular diagnosis and therapeutic procedures. Ready access is defined as ensured, timely access to a cardiac catheterization laboratory with personnel who have appropriate credentials and experience in invasive coronary procedures, as well as to emergency or urgent cardiovascular surgery and cardiac anesthesia (2,300).

The approach to the achievement of the twin goals described here includes the initiation of pharmacological management and planning of a definitive treatment strategy for the underlying disease process. Most patients are stable at presentation or stabilize after a brief period of intensive pharmacological management and, after appropriate counseling, will be able to participate in the choice of an approach for definitive therapy (see Section 3.3 for a full discussion of conservative vs. invasive strategy selection). A few patients will require prompt triage to emergency or urgent cardiac catheterization and/or the placement of an IABP.

3.1.1. General Care

The severity of symptoms dictates some of the general care that should be given during the initial treatment. Patients should be placed on bed rest while ischemia is ongoing but

can be mobilized to a chair and use a bedside commode when symptom free. Subsequent activity should not be inappropriately restrictive; instead, it should be focused on the prevention of recurrent symptoms and liberalized as judged appropriate when response to treatment occurs. Patients with cyanosis, respiratory distress, or other high-risk features should receive supplemental oxygen. Adequate arterial oxygen saturation should be confirmed with direct measurement (especially with respiratory distress or cyanosis) or pulse oximetry. No evidence is available to support the administration of oxygen to all patients with ACS in the absence of signs of respiratory distress or arterial hypoxemia. Its use based on the evidence base can be limited to those with questionable respiratory status and documented hypoxemia. Nevertheless, it is the opinion of the Writing Committee that a short period of initial routine oxygen supplementation is reasonable during initial stabilization of the patient, given its safety and the potential for underrecognition of hypoxemia. Inhaled oxygen should be administered if the arterial oxygen saturation (SaO_2) declines to less than 90%. Finger pulse oximetry is useful for the continuous monitoring of SaO_2 but is not mandatory in patients who do not appear to be at risk of hypoxemia. Patients should undergo continuous ECG monitoring during their ED evaluation and early hospital phase, because sudden, unexpected ventricular fibrillation is the major preventable cause of death in this early period. Furthermore, monitoring for the recurrence of ST-segment shifts provides useful diagnostic and prognostic information, although the system of monitoring for ST-segment shifts must include specific methods intended to provide stable and accurate recordings.

3.1.2. Use of Anti-Ischemic Therapies

3.1.2.1. NITRATES

Nitroglycerin reduces myocardial oxygen demand while enhancing myocardial oxygen delivery. Nitroglycerin, an endothelium-independent vasodilator, has both peripheral and coronary vascular effects. By dilating the capacitance vessels (i.e., the venous bed), it increases venous pooling to decrease myocardial preload, thereby reducing ventricular wall tension, a determinant of myocardial oxygen demand (MVO_2). More modest effects on the arterial circulation decrease systolic wall stress (afterload), which contributes to further reductions in MVO_2. This decrease in myocardial oxygen demand is in part offset by reflex increases in heart rate and contractility, which counteract the reductions in MVO_2 unless a beta blocker is concurrently administered. Nitroglycerin dilates normal and atherosclerotic epicardial coronary arteries and smaller arteries that constrict with certain stressors (e.g., cold, mental or physical exercise). With severe atherosclerotic coronary obstruction and with less severely obstructed vessels with endothelial dysfunction, physiological responses to changes in myocardial blood flow are often impaired (i.e., loss of flow-mediated dilation), so maximal dilation does not occur unless a direct-acting vasodilator like NTG is administered. Thus, NTG promotes the dilation of large coronary arteries, as well as collateral flow and redistribution of coronary blood flow to ischemic regions. Inhibition of platelet aggregation also occurs with NTG (300), but the clinical significance of this action is not well defined.

Intravenous NTG can benefit patients whose symptoms are not relieved in the hospital with three 0.4-mg sublingual NTG tablets taken 5 min apart (Tables 12 and 14) and with the initiation of an oral or intravenous beta blocker (when there are no contraindications), as well as those with HF or hypertension. Note that NTG is contraindicated after the use of sildenafil within the previous 24 h or tadalafil within 48 h or with hypotension (301–303). The suitable delay before nitrate administration after the use of vardenafil has not been determined, although blood pressure had generally returned to baseline by 24 h (304). These drugs inhibit the phosphodiesterase that degrades cyclic guanosine monophosphate, and cyclic guanosine monophosphate mediates vascular smooth muscle relaxation by nitric oxide. Thus, NTG-mediated vasodilatation is markedly exaggerated and prolonged in the presence of phosphodiesterase inhibitors. Nitrate use within 24 h after sildenafil or the administration of sildenafil in a patient who has received a nitrate within 24 h has been associated with profound hypotension, MI,

Table 14. NTG and Nitrates in Angina

Compound	Route	Dose/Dosage	Duration of Effect
NTG	Sublingual tablets	0.3 to 0.6 mg up to 1.5 mg	1 to 7 min
	Spray	0.4 mg as needed	Similar to sublingual tablets
	Transdermal	0.2 to 0.8 mg per h every 12 h	8 to 12 h during intermittent therapy
	Intravenous	5 to 200 mcg per min	Tolerance in 7 to 8 h
Isosorbide dinitrate	Oral	5 to 80 mg, 2 or 3 times daily	Up to 8 h
	Oral, slow release	40 mg 1 or 2 times daily	Up to 8 h
Isosorbide mononitrate	Oral	20 mg twice daily	12 to 24 h
	Oral, slow release	60 to 240 mg once daily	
Pentaerythritol tetranitrate	Sublingual	10 mg as needed	Not known
Erythritol tetranitrate	Sublingual	5 to 10 mg as needed	Not known
	Oral	10 to 30 mg 3 times daily	Not known

Adapted from Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina. Available at: http://www.acc.org/qualityandscience (4).
NTG = nitroglycerin.

and even death (303). Similar concerns apply to tadalafil and vardenafil (301,304).

Intravenous NTG may be initiated at a rate of 10 mcg per min through continuous infusion via nonabsorbing tubing and increased by 10 mcg per min every 3 to 5 min until some relief of symptoms or blood pressure response is noted. If no response is seen at 20 mcg per min, increments of 10 and, later, 20 mcg per min can be used. If symptoms and signs of ischemia are relieved, there is no need to continue to increase the dose to effect a blood pressure response. If symptoms and signs of ischemia are not relieved, the dose should be increased until a blood pressure response is observed. Once a partial blood pressure response is observed, the dosage increase should be reduced and the interval between increments lengthened. Side effects of NTG include headache and hypotension. Systolic blood pressure generally should not be titrated to less than 110 mm Hg in previously normotensive patients or to greater than 25% below the starting mean arterial blood pressure if hypertension was present. Nitroglycerin should be avoided in patients with initial systolic blood pressure less than 90 mm Hg or 30 mm Hg or more below baseline or with marked bradycardia or tachycardia. Although recommendations for a maximal dose are not available, a ceiling of 200 mcg per min is commonly used. Even prolonged (2 to 4 weeks) infusion at 300 to 400 mcg per min does not increase methemoglobin levels (306).

Topical or oral nitrates are acceptable alternatives for patients who require antianginal therapy but who do not have ongoing refractory ischemic symptoms. Tolerance to the hemodynamic effects of nitrates is dose and duration dependent and typically becomes important after 24 h of continuous therapy with any formulation. Patients who require continued intravenous NTG beyond 24 h may require periodic increases in infusion rate to maintain efficacy. An effort must be made to use non–tolerance-producing nitrate regimens (lower doses and intermittent dosing). When patients have been free of ischemic discomfort and other manifestations of ischemia for 12 to 24 h, an attempt should be made to reduce the dose of intravenous NTG and to switch to oral or topical nitrates. It is not appropriate to continue intravenous NTG in patients who remain free of signs and symptoms of ischemia. When ischemia recurs during continuous intravenous NTG therapy, responsiveness to nitrates can often be restored by increasing the dose and, after symptoms have been controlled for several hours, attempting to add a nitrate-free interval. This strategy should be pursued as long as symptoms are not adequately controlled. In stabilized patients, intravenous NTG should generally be converted within 24 h to a nonparenteral alternative (Table 14) administered in a non–tolerance-producing regimen to avoid the potential reactivation of symptoms. A practical method for converting intravenous to topical NTG has been published (307).

Most studies of nitrate treatment in UA/NSTEMI have been small and uncontrolled, and there are no randomized, placebo-controlled trials that address either symptom relief or reduction in cardiac events. One small randomized trial compared intravenous NTG with buccal NTG and found no significant difference in the control of ischemia (308). An overview of small studies of NTG in MI from the prefibrinolytic era suggested a 35% reduction in mortality rates (309); in contrast, both the Fourth International Study of Infarct Survival (ISIS-4) (310) and Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico (GISSI-3) (311) trials formally tested this hypothesis in patients with suspected MI in the reperfusion era and failed to confirm this magnitude of benefit. However, these large trials are confounded by frequent prehospital and hospital use of NTG in the "control" groups. Nevertheless, a strategy of routine as opposed to selective use of nitrates did not reduce mortality. The abrupt cessation of intravenous NTG has been associated with exacerbation of ischemic changes on the ECG (312), and a graded reduction in the dose of intravenous NTG is advisable. Thus, the rationale for NTG use in UA/NSTEMI is extrapolated from pathophysiological principles and extensive, although uncontrolled, clinical observations (300).

3.1.2.2. MORPHINE SULFATE

Morphine sulfate (1 to 5 mg IV) is reasonable for patients whose symptoms are not relieved despite NTG (e.g., after 3 serial sublingual NTG tablets) or whose symptoms recur despite adequate anti-ischemic therapy. Unless contraindicated by hypotension or intolerance, morphine may be administered with intravenous NTG, with careful blood pressure monitoring, and may be repeated every 5 to 30 min as needed to relieve symptoms and maintain patient comfort.

Morphine sulfate has potent analgesic and anxiolytic effects, as well as hemodynamic effects, that are potentially beneficial in UA/NSTEMI. No randomized trials have defined the unique contribution of morphine to the initial therapeutic regimen or its optimal administration schedule. Morphine causes venodilation and can produce modest reductions in heart rate (through increased vagal tone) and systolic blood pressure to further reduce myocardial oxygen demand. The major adverse reaction to morphine is an exaggeration of its therapeutic effect, causing hypotension, especially in the presence of volume depletion and/or vasodilator therapy. This reaction usually responds to supine or Trendelenburg positioning or intravenous saline boluses and atropine when accompanied by bradycardia; it rarely requires pressors or naloxone to restore blood pressure. Nausea and vomiting occur in approximately 20% of patients. Respiratory depression is the most serious complication of morphine; severe hypoventilation that requires intubation occurs very rarely in patients with UA/NSTEMI treated with morphine. Naloxone (0.4 to 2.0 mg IV) may be administered for morphine overdose with respiratory or circulatory depression. Other narcotics may be considered in patients allergic to morphine. A cautionary note on mor-

phine use has been raised by data from a large observational registry (n = 443 hospitals) that enrolled patients with UA/NSTEMI (n = 57,039) (313). Those receiving morphine (30%) had a higher adjusted likelihood of death (propensity-adjusted OR = 1.41, 95% CI 1.26 to 1.57), which persisted across all subgroups (313). Although subject to uncontrolled selection biases, these results raise a safety concern and suggest the need for a randomized trial. Meanwhile, the Writing Committee has downgraded the recommendation for morphine use for uncontrolled ischemic chest discomfort from a Class I to a Class IIa recommendation.

3.1.2.3. BETA-ADRENERGIC BLOCKERS

Beta blockers competitively block the effects of catecholamines on cell membrane beta receptors. Beta-1 adrenergic receptors are located primarily in the myocardium; inhibition of catecholamine action at these sites reduces myocardial contractility, sinus node rate, and AV node conduction velocity. Through these actions, they blunt the heart rate and contractility responses to chest pain, exertion, and other stimuli. They also decrease systolic blood pressure. All of these effects reduce MVO_2. Beta-2 adrenergic receptors are located primarily in vascular and bronchial smooth muscle; the inhibition of catecholamine action at these sites produces vasoconstriction and bronchoconstriction (300). In UA/NSTEMI, the primary benefits of beta blockers are due to inhibition of beta-1 adrenergic receptors, which results in a decrease in cardiac work and myocardial oxygen demand. Slowing of the heart rate also has a favorable effect, acting not only to reduce MVO_2 but also to increase the duration of diastole and diastolic pressure-time, a determinant of forward coronary flow and collateral flow.

Beta blockers, administered orally, should be started early in the absence of contraindications. Intravenous administration may be warranted in patients with ongoing rest pain, especially with tachycardia or hypertension, in the absence of contraindications (see below) (Table 12).

The benefits of routine early intravenous use of beta blockers in the fibrinolytic era have been challenged by 2 later randomized trials of intravenous beta blockade (314,315) and by a post hoc analysis of the use of atenolol in the GUSTO-I trial (316). A subsequent systematic review of early beta-blocker therapy in STEMI found no significant reduction in mortality (27). Most recently, the utility of early intravenous followed by oral beta blockade (metoprolol) was tested in 45,852 patients with MI (93% had STEMI, 7% had NSTEMI) in the COMMIT study (317). Neither the composite of death, reinfarction, or cardiac arrest nor death alone was reduced for up to 28 d in the hospital. Overall, a modest reduction in reinfarction and ventricular fibrillation (which was seen after day 1) was counterbalanced by an increase in cardiogenic shock, which occurred early (first day) and primarily in those who were hemodynamically compromised or in HF or who were stable but at high risk of development of shock. Thus, early aggressive beta blockade poses a substantial net hazard in hemodynamically unstable patients and should be avoided. Risk factors for shock were older age, female sex, time delay, higher Killip class, lower blood pressure, higher heart rate, ECG abnormality, and previous hypertension. There was a moderate net benefit for those who were relatively stable and at low risk of shock. Whether to start beta blockade intravenously or orally in these latter stable patients is unclear, and patterns of use vary. In an attempt to balance the evidence base overall for UA/NSTEMI patients, beta blockers are recommended in these guidelines to be initiated orally, in the absence of contraindications (e.g., HF), within the first 24 h. Greater caution is now suggested in the early use of intravenous beta blockers, which should be targeted to specific indications and should be avoided with HF, hypotension, and hemodynamic instability.

The choice of beta blocker for an individual patient is based primarily on pharmacokinetic and side effect criteria, as well as on physician familiarity (Table 15). There are no comparative studies between members of this class in the

Table 15. Properties of Beta Blockers in Clinical Use

Drugs	Selectivity	Partial Agonist Activity	Usual Dose for Angina
Propranolol	None	No	20 to 80 mg twice daily
Metoprolol	$Beta_1$	No	50 to 200 mg twice daily
Atenolol	$Beta_1$	No	50 to 200 mg per d
Nadolol	None	No	40 to 80 mg per d
Timolol	None	No	10 mg twice daily
Acebutolol	$Beta_1$	Yes	200 to 600 mg twice daily
Betaxolol	$Beta_1$	No	10 to 20 mg per d
Bisoprolol	$Beta_1$	No	10 mg per d
Esmolol (intravenous)	$Beta_1$	No	50 to 300 mcg per kg per min
Labetalol*	None	Yes	200 to 600 mg twice daily
Pindolol	None	Yes	2.5 to 7.5 mg 3 times daily
Carvedilol	None	Yes	6.25 mg twice daily, uptitrated to a maximum of 25 mg twice daily

*Labetalol and carvedilol are combined alpha and beta blockers. Adapted from Table 25, Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina. Available at: http://www.acc.org/qualityandscience (4).

acute setting. Beta blockers without intrinsic sympathomimetic activity are preferred, however. Agents studied in the acute setting include metoprolol, propranolol, and atenolol. Carvedilol may be added to the list of agents studied for post-MI use. Comparative studies among different beta blockers in the chronic setting after UA/NSTEMI also are not available to establish a preference among agents. In patients with HF, 1 study suggested greater benefit with carvedilol, with mixed beta-blocking and alpha-adrenergic-blocking effects, than metoprolol, a relatively selective beta-1 blocker (318). In patients with hypertension, the relative cardiovascular benefit of atenolol has been questioned on the basis of recent clinical trial analyses (319,320).

Patients with marked first-degree AV block (i.e., ECG PR interval greater than 0.24 s), any form of second- or third-degree AV block in the absence of a functioning implanted pacemaker, a history of asthma, severe LV dysfunction or HF (e.g., rales or S_3 gallop) or at high risk for shock (see above) should not receive beta blockers on an acute basis (4). Patients with evidence of a low-output state (e.g., oliguria) or sinus tachycardia, which often reflects low stroke volume, significant sinus bradycardia (heart rate less than 50 beats per min), or hypotension (systolic blood pressure less than 90 mm Hg) should not receive acute beta-blocker therapy until these conditions have resolved. Patients at highest risk for cardiogenic shock due to intravenous beta blockade in the COMMIT trial were those with tachycardia or in Killip Class II or III (317). However, beta blockers are strongly recommended before discharge in those with compensated HF or LV systolic dysfunction for secondary prevention (321). Patients with significant chronic obstructive pulmonary disease who may have a component of reactive airway disease should be given beta blockers very cautiously; initially, low doses of a beta-1–selective agent should be used. If there are concerns about possible intolerance to beta blockers, initial selection should favor a short-acting beta-1–specific drug such as metoprolol or esmolol. Mild wheezing or a history of chronic obstructive pulmonary disease mandates a short-acting cardioselective agent at a reduced dose (e.g., 12.5 mg of metoprolol orally) rather than the complete avoidance of a beta blocker.

In the absence of these concerns, previously studied regimens may be used. Intravenous metoprolol may be given in 5-mg increments by slow intravenous administration (5 mg over 1 to 2 min), repeated every 5 min for a total initial dose of 15 mg. In patients who tolerate the total 15-mg IV dose, oral therapy can be initiated 15 min after the last intravenous dose at 25 to 50 mg every 6 h for 48 h. Thereafter, patients should receive a maintenance dose of up to 100 mg twice daily. Alternatively, intravenous propranolol may be administered as an initial dose of 0.5 to 1.0 mg, followed in 1 to 2 h by 40 to 80 mg by mouth every 6 to 8 h. Monitoring during intravenous beta-blocker therapy should include frequent checks of heart rate and blood pressure and continuous ECG monitoring, as well as auscultation for rales and bronchospasm. Beta blockade also may be started orally, in smaller initial doses if appropriate, within the first 24 h, in cases in which a specific clinical indication for intravenous initiation is absent or the safety of aggressive early beta blockade is a concern. Carvedilol, 6.25 mg by mouth twice daily, uptitrated individually at 3- to 10-d intervals to a maximum of 25 mg twice daily, can reduce mortality and reinfarction when given to patients with recent (3 to 21 d) MI and LV dysfunction (321). After the initial intravenous load, if given, patients without limiting side effects may be converted to an oral regimen. The target resting heart rate is 50 to 60 beats per minute unless a limiting side effect is reached. Selection of the oral agent should include the clinician's familiarity with the agent. Maintenance doses are given in Table 15.

Initial studies of beta-blocker benefits in ACS were small and uncontrolled. An overview of double-blind, randomized trials in patients with threatening or evolving MI suggests an approximately 13% reduction in the risk of progression to MI (322). These trials were conducted prior to the routine use of ASA, heparin, clopidogrel, GP IIb/IIIa inhibitors, and revascularization. These trials lack sufficient power to assess the effects of these drugs on mortality rates for UA. Pooled results from the Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC), Evaluation of PTCA and Improve Long-term Outcome by c7E3 GP IIb/IIIa receptor blockade (EPILOG), Evaluation of Platelet IIb/IIIa Inhibitor for STENTing (EPISTENT), CAPTURE, and ReoPro in Acute myocardial infarction and Primary PTCA Organization and Randomization Trial (RAPPORT) studies were used to evaluate the efficacy of beta-blocker therapy in patients with ACS who were undergoing PCI (323). At 30 d, death occurred in 0.6% of patients receiving beta-blocker therapy versus 2.0% of patients not receiving such therapy (p less than 0.001). At 6 months, death occurred in 1.7% of patients receiving beta-blocker therapy versus 3.7% not receiving this therapy (p less than 0.001). Thus, patients receiving beta-blocker therapy who undergo PCI for UA or MI have a lower short-term mortality (323).

Overall, the rationale for beta-blocker use in all forms of CAD, including UA, is generally favorable, with the exception of initial HF. In the absence of contraindications, the new evidence appears sufficient to make beta blockers a routine part of care. A related group shown to benefit are high- or intermediate-risk patients who are scheduled to undergo cardiac or noncardiac surgery (324). A recent exception to beta-blocker benefit was COMMIT, a large trial of mostly STEMI patients, which showed no overall mortality effect. Subgroup analysis suggested this to be due to an increased risk in those with initial HF or risk factors for cardiogenic shock (317). In contrast to this adverse experience with early, aggressive beta blockade, carvedilol, begun in low doses 3 to 10 d after MI in patients with LV dysfunction (ejection fraction of 0.40 or less) and gradually uptitrated, decreased subsequent death or nonfatal recurrent MI when given in conjunction with modern ACS therapies

in the most contemporary oral beta blocker post-MI trial, CAPRICORN (Carvedilol Post-Infarct Survival Control in LV Dysfunction) (321).

In conclusion, evidence for the beneficial effects of the use of beta blockers in patients with UA is based on limited randomized trial data along with pathophysiological considerations and extrapolation from experience with CAD patients who have other types of ischemic syndromes (stable angina or compensated chronic HF). The duration of benefit with long-term oral therapy is uncertain and likely varies with the extent of revascularization.

3.1.2.4. CALCIUM CHANNEL BLOCKERS

Calcium channel blockers (CCBs) reduce cell transmembrane inward calcium flux, which inhibits both myocardial and vascular smooth muscle contraction; some also slow AV conduction and depress sinus node impulse formation. Agents in this class vary in the degree to which they produce vasodilation, decreased myocardial contractility, AV block, and sinus node slowing. Nifedipine and amlodipine have the most peripheral arterial dilatory effects but few or no AV or sinus node effects, whereas verapamil and diltiazem have prominent AV and sinus node effects and some peripheral arterial dilatory effects as well. All 4 of these agents, as well as other approved agents, have coronary dilatory properties that appear to be similar. Although different CCBs are structurally and, potentially, therapeutically diverse, superiority of 1 agent over another in UA/NSTEMI has not been demonstrated, except for the increased risks posed by rapid-release, short-acting dihydropyridines such as nifedipine (Table 16). Beneficial effects in UA/NSTEMI are believed to be due to variable combinations of decreased myocardial oxygen demand (related to decreased afterload, contractility, and heart rate) and improved myocardial flow (related to coronary arterial and arteriolar dilation) (300,325). These agents also have theoretically beneficial effects on LV relaxation and arterial compliance. Major side effects include hypotension, worsening HF, bradycardia, and AV block.

Calcium channel blockers may be used to control ongoing or recurring ischemia-related symptoms in patients who already are receiving adequate doses of nitrates and beta blockers, in patients who are unable to tolerate adequate doses of 1 or both of these agents, and in patients with variant angina (see Section 6.7). In addition, these drugs have been used for the management of hypertension in patients with recurrent UA (325). Rapid-release, short-acting dihydropyridines (e.g., nifedipine) must be avoided in the absence of concomitant beta blockade because of increased adverse potential (326,327,328). Verapamil and diltiazem should be avoided in patients with pulmonary edema or evidence of severe LV dysfunction (329–331). Amlodipine and felodipine are reasonably well tolerated by patients with mild LV dysfunction (329–331,332–334), although their use in UA/NSTEMI has not been studied. The CCB evidence base in UA/NSTEMI is greatest for verapamil and diltiazem (328,331).

Several randomized trials during the 1980s tested CCBs in UA/NSTEMI and found that they relieve or prevent signs and symptoms of ischemia to a degree similar to the beta blockers. The Danish Study Group on Verapamil in Myocardial Infarction (DAVIT) (332,333) studied 3,447 patients with suspected UA/NSTEMI. A benefit was not proved, but death or nonfatal MI tended to be reduced. The Diltiazem Reinfarction Study (DRS) studied 576 patients with UA/NSTEMI (329). Diltiazem reduced reinfarction and refractory angina at 14 d without an increase in

Table 16. Properties of Calcium Channel Blockers in Clinical Use

Drug	Usual Dose	Duration of Action	Side Effects
Dihydropyridines			
Nifedipine*	Immediate release: 30 to 90 mg daily orally	Short	Hypotension, dizziness, flushing, nausea, constipation, edema
	Slow release: 30 to 180 mg orally		
Amlodipine	5 to 10 mg once daily	Long	Headache, edema
Felodipine	5 to 10 mg once daily	Long	Headache, edema
Isradipine	2.5 to 10 mg twice daily	Medium	Headache, fatigue
Nicardipine	20 to 40 mg 3 times daily	Short	Headache, dizziness, flushing, edema
Nisoldipine	20 to 40 mg once daily	Short	Similar to nifedipine
Nitrendipine	20 mg once or twice daily	Medium	Similar to nifedipine
Miscellaneous			
Diltiazem	Immediate release: 30 to 90 mg 4 times daily	Short	Hypotension, dizziness, flushing, bradycardia, edema
	Slow release: 120 to 360 mg once daily	Long	
Verapamil	Immediate release: 80 to 160 mg 3 times daily	Short	Hypotension, myocardial depression, heart failure, edema, bradycardia
	Slow release: 120 to 480 mg once daily	Long	

*Immediate-release nifedipine not recommended for UA/NSTEMI except with concomitant beta blockade. Modified from Table 27 in Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina. Available at: http://www.acc.org/qualityandscience (4).

mortality rates. Retrospective analysis of the non–Q-wave MI subset of patients in the Multicenter Diltiazem Postinfarction Trial (MDPIT) suggested similar findings (334). The Holland Interuniversity Nifedipine/metoprolol Trial (HINT), tested nifedipine and metoprolol in a 2 × 2 factorial design in 515 patients (327). The study was stopped early because of concern for harm with the use of nifedipine alone. In contrast, patients already taking a beta blocker appeared to benefit from the addition of nifedipine (risk ratio [RR] 0.68) (335).

Meta-analyses combining UA/NSTEMI studies of all CCBs have suggested no overall benefit (322,336), whereas those excluding nifedipine (e.g., for verapamil alone) have reported favorable effects on outcomes (332). Retrospective analyses of DAVIT and MDPIT suggested that verapamil and diltiazem can have a detrimental effect on mortality rates in patients with LV dysfunction (329,330). In contrast, verapamil reduced diuretic use in DAVIT-2, (333). Furthermore, subsequent prospective trials with verapamil administered to MI patients with HF who were receiving an ACE inhibitor suggested a benefit (330,337). The Diltiazem as Adjunctive Therapy to Activase (DATA) trial also suggested that intravenous diltiazem in MI patients can be safe; death, MI, and recurrent ischemia were decreased at 35 d and 6 months (338).

In summary, definitive evidence for a benefit of CCBs in UA/NSTEMI is predominantly limited to symptom control. For immediate-release nifedipine, an increase in serious events is suggested when administered early without a beta blocker. The heart rate–slowing CCB drugs (verapamil and diltiazem) can be administered early to patients with UA/NSTEMI without HF without overall harm and with trends toward a benefit. Therefore, when beta blockers cannot be used, and in the absence of clinically significant LV dysfunction, heart rate–slowing CCBs are preferred. Greater caution is indicated when combining a beta blocker and CCB for refractory ischemic symptoms, because they may act in synergy to depress LV function and sinus and AV node conduction. The risks and benefits in UA/NSTEMI of newer CCBs, such as the dihydropyridines amlodipine and felodipine, relative to the older agents in this class that have been reviewed here, remain undefined, which suggests a cautious approach, especially in the absence of beta blockade.

3.1.2.5. INHIBITORS OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Angiotensin-converting enzyme inhibitors have been shown to reduce mortality rates in patients with MI or who recently had an MI and have LV systolic dysfunction (339–341), in patients with diabetes mellitus with LV dysfunction (342), and in a broad spectrum of patients with high-risk chronic CAD, including patients with normal LV function (343). Follow-up of patients with LV dysfunction after MI in the TRACE (TRAndolapril Cardiac Evaluation) trial showed that the beneficial effect of trandolapril on mortality and hospitalization rate was maintained for at least 10 to 12 years (344). A systematic review assessing potential ASA–ACE inhibitor interactions showed clinically important benefits with ACE inhibitor therapy, irrespective of whether concomitant ASA was used, and only weak evidence of a reduction in the benefit of ACE inhibitor therapy added to ASA (345); these data did not solely involve patients with MI. Accordingly, ACE inhibitors should be used in patients receiving ASA and in those with hypertension that is not controlled with beta blockers. Recent data on ACE inhibitor patients with stable CAD are summarized in the section on long-term medical therapy (see Section 5.2.3).

In patients with MI complicated by LV systolic dysfunction, HF, or both, the angiotensin receptor blocker valsartan was as effective as captopril in patients at high risk for cardiovascular events after MI. The combination of valsartan and captopril increased adverse events and did not improve survival (346). Although not in the acute care setting, treatment of patients with chronic HF with candesartan (at least half of whom had an MI) in the CHARM (Candesartan in Heart failure Assessment in Reduction of Mortality)-Overall program showed a reduction in cardiovascular deaths and hospital admissions for HF, independent of ejection fraction or baseline treatment (347).

The selective aldosterone receptor blocker eplerenone, used in patients with MI complicated by LV dysfunction and either HF or diabetes mellitus, reduced morbidity and mortality in the Eplerenone Post-acute myocardial infarction Heart failure Efficacy and SUrvival Study (EPHESUS) (348). This complements data from the earlier Randomized ALdactone Evaluation Study (RALES), in which aldosterone receptor blockade with spironolactone decreased morbidity and death in patients with severe HF, half of whom had an ischemic origin (349). Indications for long-term use of aldosterone receptor blockers are given in Section 5.2.3.

3.1.2.6. OTHER ANTI-ISCHEMIC THERAPIES

Other less extensively studied therapies for the relief of ischemia, such as spinal cord stimulation (350) and prolonged external counterpulsation (351,352), are under evaluation. Most experience has been gathered with spinal cord stimulation in "intractable angina" (353), in which anginal relief has been described. They have not been applied in the acute setting for UA/NSTEMI.

The K_{ATP} channel openers have hemodynamic and cardioprotective effects that could be useful in UA/NSTEMI. Nicorandil is such an agent that has been approved in a number of countries but not in the United States. In a pilot double-blind, placebo-controlled study of 245 patients with UA, the addition of this drug to conventional treatment significantly reduced the number of episodes of transient myocardial ischemia (mostly silent) and of ventricular and supraventricular tachycardia (354). Further evaluation of this class of agents is underway.

Ranolazine is a newly approved (January 2006) agent that exerts antianginal effects without reducing heart rate or blood pressure (355). Currently, ranolazine is indicated alone or in combination with amlodipine, beta-blockers, or nitrates for the treatment of chronic angina that has failed to respond to standard antianginal therapy. The recommended initial dose is 500 mg orally twice daily, which can be escalated as needed to a maximum of 1000 mg twice daily. The mechanism of action of ranolazine has not been fully characterized but appears to depend on membrane ion-channel effects (similar to those after chronic amiodarone) (356). It is contraindicated in patients with QT-prolonging conditions. Preliminary results of a large (N = 6,560) patient trial of ranolazine, begun within 48 h of UA/NSTEMI, suggested safety and symptom relief (reduction in angina) but did not achieve the primary efficacy end point of a reduction in the composite of cardiovascular death, MI, or recurrent ischemia (hazard ratio [HR] 0.92, 95% CI 0.83 to 1.02) (357,357a). Thus, ranolazine may be safely administered for symptom relief after UA/NSTEMI, but it does not appear to significantly improve the underlying disease substrate.

3.1.2.7. INTRA-AORTIC BALLOON PUMP COUNTERPULSATION

Experience with IABP for refractory ischemia dates back more than 30 years. In a prospective registry of 22,663 IABP patients, 5,495 of whom had acute MI, placement of an IABP in MI patients primarily was performed for cardiogenic shock, for hemodynamic support during catheterization and/or angioplasty, before high-risk surgery, for mechanical complications of MI, or for refractory post-MI UA. Balloon insertions were successful in 97.7% of patients, and major complications occurred in 2.7% of patients during a median use of 3 d (358). The placement of an IABP could be useful in patients with recurrent ischemia despite maximal medical management and in those with hemodynamic instability until coronary angiography and revascularization can be completed.

3.1.2.8. ANALGESIC THERAPY

Because of the known increased risk of cardiovascular events among patients taking COX-2 inhibitors and NSAIDs (359–361), patients who are taking them at the time of UA/NSTEMI should discontinue them immediately (see Section 5.2.16 for additional discussion). A secondary analysis of the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (EXTRACT)-TIMI-25 data (362) demonstrated an increased risk of death, reinfarction, HF, or shock among patients who were taking NSAIDs within 7 d of enrollment. Longer term management is considered in Section 5.2.16.

3.2. Recommendations for Antiplatelet/Anticoagulant Therapy in Patients for Whom Diagnosis of UA/NSTEMI Is Likely or Definite

Recommendations are written as the reader follows the algorithms for antiplatelet/anticoagulant therapy and triage for angiography (Figs. 7, 8, and 9). Letters after recommendations refer to the specific box in the algorithm. See Table 13 for dosing recommendations.

3.2.1. Antiplatelet Therapy Recommendations

CLASS I

1. Aspirin should be administered to UA/NSTEMI patients as soon as possible after hospital presentation and continued indefinitely in patients not known to be intolerant of that medication. *(Level of Evidence: A)* (Figs. 7 and 8; Box A)
2. Clopidogrel (loading dose followed by daily maintenance dose)* should be administered to UA/NSTEMI patients who are unable to take ASA because of hypersensitivity or major gastrointestinal intolerance. *(Level of Evidence: A)* (Figs. 7 and 8; Box A)
3. In UA/NSTEMI patients with a history of gastrointestinal bleeding, when ASA and clopidogrel are administered alone or in combination, drugs to minimize the risk of recurrent gastrointestinal bleeding (e.g., proton-pump inhibitors) should be prescribed concomitantly. *(Level of Evidence: B)*
4. For UA/NSTEMI patients in whom an initial invasive strategy is selected, antiplatelet therapy in addition to aspirin should be initiated before diagnostic angiography (upstream) with either clopidogrel (loading dose followed by daily maintenance dose)* or an intravenous GP IIb/IIIa inhibitor. *(Level of Evidence: A)* Abciximab as the choice for upstream GP IIb/IIIa therapy is indicated only if there is no appreciable delay to angiography and PCI is likely to be performed; otherwise, IV eptifibatide or tirofiban is the preferred choice of GP IIb/IIIa inhibitor. *(Level of Evidence: B)*
5. For UA/NSTEMI patients in whom an initial conservative (i.e., noninvasive) strategy is selected (see Section 3.3), clopidogrel (loading dose followed by daily maintenance dose)* should be added to ASA and anticoagulant therapy as soon as possible after admission and administered for at least 1 month *(Level of Evidence: A)* and ideally up to 1 year. *(Level of Evidence: B)* (Fig. 8; Box C2)
6. For UA/NSTEMI patients in whom an initial conservative strategy is selected, if recurrent symptoms/ischemia, HF, or serious arrhythmias subsequently appear, then diagnostic angiography should be performed. *(Level of Evidence: A)* (Fig. 8; Box D) Either an intravenous GP IIb/IIIa inhibitor (eptifibatide or tirofiban; *Level of Evidence: A*) or clopidogrel (loading dose followed by daily maintenance dose; *Level of Evidence: A*)* should be added to ASA and anticoagulant therapy before diagnostic angiography (upstream). *(Level of Evidence: C)*

CLASS IIa

1. For UA/NSTEMI patients in whom an initial conservative strategy is selected and who have recurrent ischemic discomfort with clopidogrel, ASA, and anticoagulant therapy, it is reasonable to add a GP IIb/IIIa antagonist before diagnostic angiography. *(Level of Evidence: C)*
2. For UA/NSTEMI patients in whom an initial invasive strategy is selected, it is reasonable to initiate antiplatelet therapy with both

*Some uncertainty exists about optimum dosing of clopidogrel. Randomized trials establishing its efficacy and providing data on bleeding risks used a loading dose of 300 mg orally followed by a daily oral maintenance dose of 75 mg. Higher oral loading doses such as 600 or 900 mg of clopidogrel more rapidly inhibit platelet aggregation and achieve a higher absolute level of inhibition of platelet aggregation, but the additive clinical efficacy and the safety of higher oral loading doses have not been rigorously established.

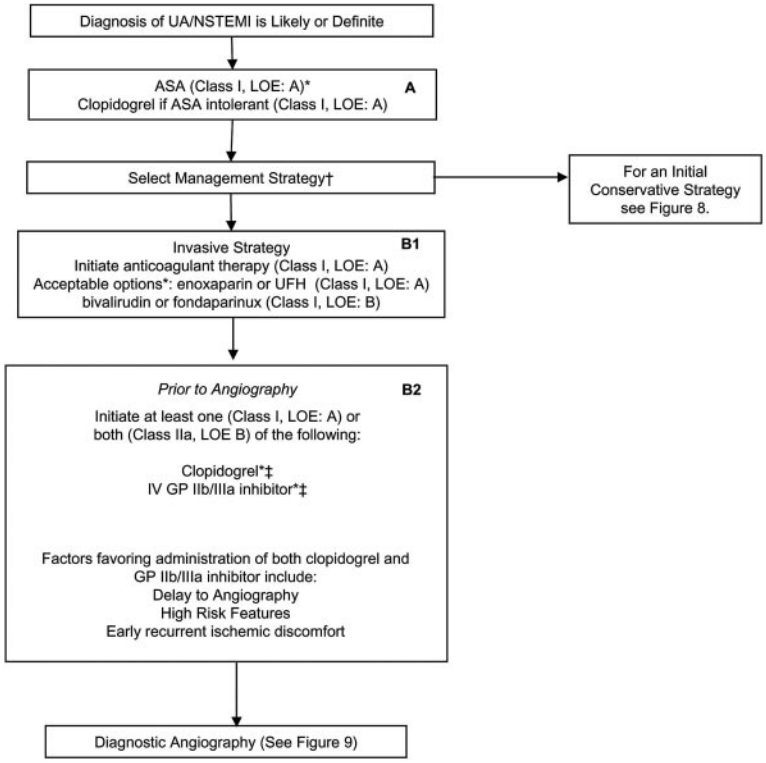


Figure 7. Algorithm for Patients With UA/NSTEMI Managed by an Initial Invasive Strategy

When multiple drugs are listed, they are in alphabetical order and not in order of preference (e.g., Boxes B1 and B2). *See dosing Table 13. †See Table 11 for selection of management strategy. ‡Evidence exists that GP IIb/IIIa inhibitors may not be necessary if the patient received a preloading dose of at least 300 mg of clopidogrel at least 6 h earlier (Class I, Level of Evidence B for clopidogrel administration) and bivalirudin is selected as the anticoagulant (Class IIa, Level of Evidence B). ASA = aspirin; GP = glycoprotein; IV = intravenous; LOE = level of evidence; UA/NSTEMI = unstable angina/non–ST-elevation myocardial infarction; UFH = unfractionated heparin.

clopidogrel (loading dose followed by daily maintenance dose)* and an intravenous GP IIb/IIIa inhibitor. *(Level of Evidence: B)* Abciximab as the choice for upstream GP IIb/IIIa therapy is indicated only if there is no appreciable delay to angiography and PCI is likely to be performed; otherwise, IV eptifibatide or tirofiban is the preferred choice of GP IIb/IIIa inhibitor.† *(Level of Evidence: B)*

3. For UA/NSTEMI patients in whom an initial invasive strategy is selected, it is reasonable to omit upstream administration of an intravenous GP IIb/IIIa antagonist before diagnostic angiography if bivalirudin is selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least 6 h earlier than planned catheterization or PCI. *(Level of Evidence: B)*

CLASS IIb

For UA/NSTEMI patients in whom an initial conservative (i.e., noninvasive) strategy is selected, it may be reasonable to add eptifibatide or tirofiban to anticoagulant and oral antiplatelet therapy. *(Level of Evidence: B)* (Fig. 8; Box C2)

*Some uncertainty exists about optimum dosing of clopidogrel. Randomized trials establishing its efficacy and providing data on bleeding risks used a loading dose of 300 mg orally followed by a daily oral maintenance dose of 75 mg. Higher oral loading doses such as 600 or 900 mg of clopidogrel may more rapidly inhibit platelet aggregation and achieve a higher absolute level of inhibition of platelet aggregation, but the additive efficacy and the safety of higher oral loading doses have not been rigorously established.

†Factors favoring administration of both clopidogrel and GP IIb/IIIa inhibitor include: delay to angiography, high-risk features, and early recurrent ischemic discomfort.

CLASS III

Abciximab should not be administered to patients in whom PCI is not planned. *(Level of Evidence: A)*

3.2.2. Anticoagulant Therapy Recommendations

CLASS I

Anticoagulant therapy should be added to antiplatelet therapy in UA/NSTEMI patients as soon as possible after presentation.

a. For patients in whom an invasive strategy is selected, regimens with established efficacy at a *Level of Evidence: A* include enoxaparin and UFH (Fig. 7; Box B1), and those with established efficacy at a *Level of Evidence: B* include bivalirudin and fondaparinux (Fig. 7; Box B1).

b. For patients in whom a conservative strategy is selected, regimens using either enoxaparin‡ or UFH *(Level of Evidence: A)* or fondaparinux *(Level of Evidence: B)* have established efficacy. (Fig. 8; Box C1) ‡See also Class IIa recommendation below.

c. In patients in whom a conservative strategy is selected and who have an increased risk of bleeding, fondaparinux is preferable. *(Level of Evidence: B)* (Fig. 8; Box C1)

CLASS IIa

For UA/NSTEMI patients in whom an initial conservative strategy is selected, enoxaparin‡ or fondaparinux is preferable to UFH as anticoagulant therapy, unless CABG is planned within 24 h. *(Level of Evidence: B)*

‡Limited data are available for the use of other LMWHs (e.g., dalteparin; see Tables 13 and 17) in UA/NSTEMI.

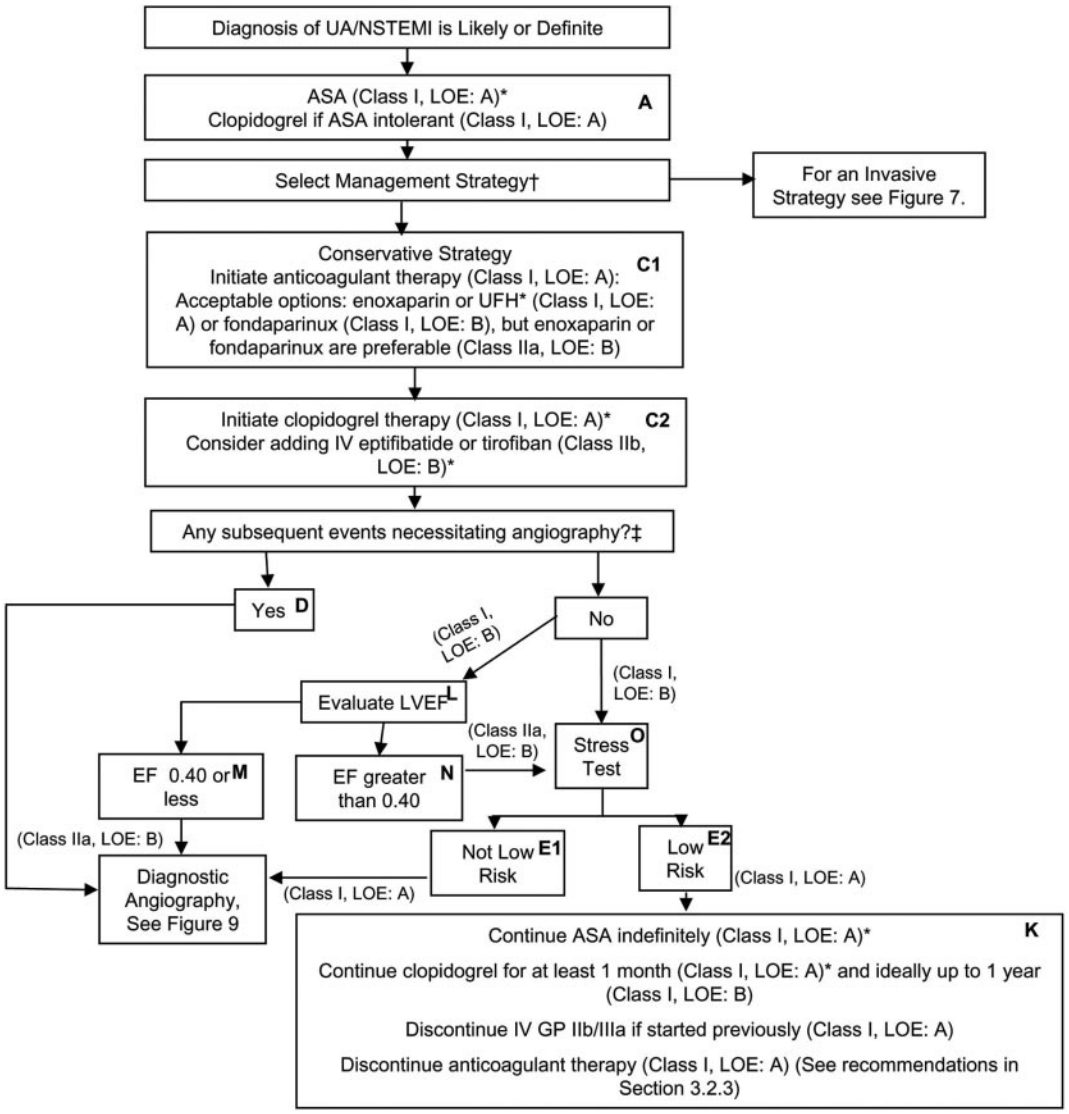


Figure 8. Algorithm for Patients With UA/NSTEMI Managed by an Initial Conservative Strategy

When multiple drugs are listed, they are in alphabetical order and not in order of preference (e.g., Boxes C1 and C2). *See dosing Table 13. †See Table 11 for selection of management strategy. ‡Recurrent symptoms/ischemia, heart failure, serious arrhythmia. ASA = aspirin; EF = ejection fraction; GP = glycoprotein; IV = intravenous; LOE = level of evidence; LVEF = left ventricular ejection fraction; UA/NSTEMI = unstable angina/non–ST-elevation myocardial infarction; UFH = unfractionated heparin.

3.2.3. Additional Management Considerations for Antiplatelet and Anticoagulant Therapy

CLASS I

1. For UA/NSTEMI patients in whom an initial conservative strategy is selected and no subsequent features appear that would necessitate diagnostic angiography (recurrent symptoms/ischemia, HF, or serious arrhythmias), a stress test should be performed. *(Level of Evidence: B)* (Fig. 8; Box O)
   a. If, after stress testing, the patient is classified as not at low risk, diagnostic angiography should be performed. *(Level of Evidence: A)* (Fig. 8; Box E1)
   b. If, after stress testing, the patient is classified as being at low risk (Fig. 8; Box E2), the instructions noted below should be followed in preparation for discharge (Fig. 8; Box K) *(Level of Evidence: A)*:
      1. Continue ASA indefinitely. *(Level of Evidence: A)*
      2. Continue clopidogrel for at least 1 month *(Level of Evidence: A)* and ideally up to 1 year. *(Level of Evidence: B)*
      3. Discontinue intravenous GP IIb/IIIa inhibitor if started previously. *(Level of Evidence: A)*
      4. Continue UFH for 48 h or administer enoxaparin or fondaparinux for the duration of hospitalization, up to 8 d, and then discontinue anticoagulant therapy. *(Level of Evidence: A)*
2. For UA/NSTEMI patients in whom CABG is selected as a postangiography management strategy, the instructions noted below should be followed (Fig. 9; Box G).

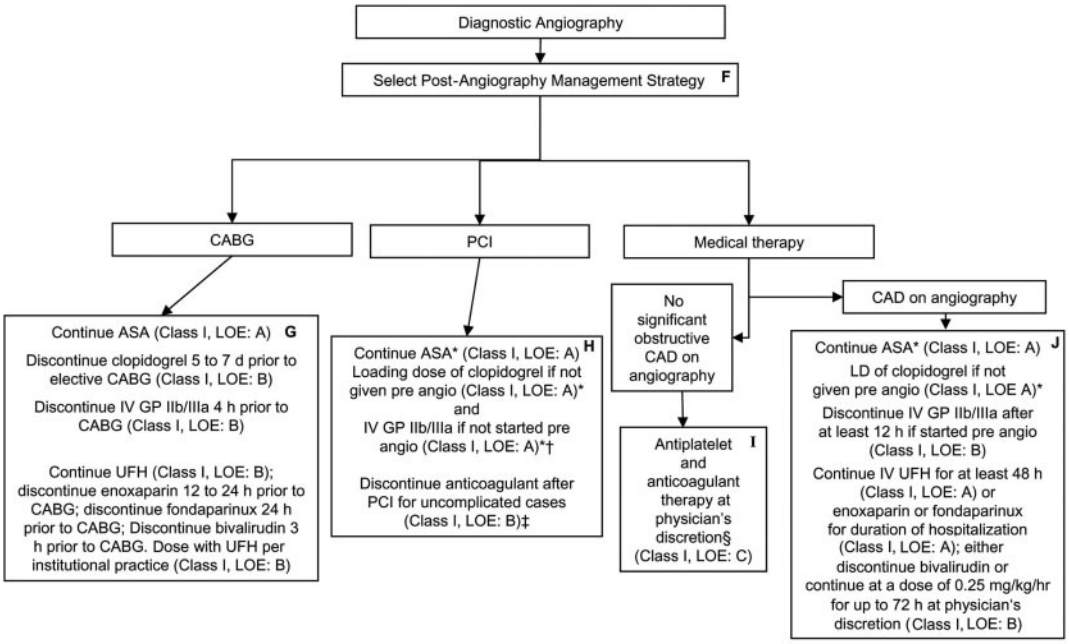


Figure 9. Management After Diagnostic Angiography in Patients With UA/NSTEMI

*See dosing Table 13. †Evidence exists that GP IIb/IIIa inhibitors may not be necessary if the patient received a preloading dose of at least 300 mg of clopidogrel at least 6 h earlier (Class I, Level of Evidence B for clopidogrel administration) and bivalirudin is selected as the anticoagulant (Class IIa, Level of Evidence B). ‡Additional bolus of UFH is recommended if fondaparinux is selected as the anticoagulant (see dosing Table 13). §For patients in whom the clinician believes coronary atherosclerosis is present, albeit without any significant, flow-limiting stenoses, long-term treatment with antiplatelet agents and other secondary prevention measures should be considered. ASA = aspirin; CABG = coronary artery bypass graft; CAD = coronary artery disease; GP = glycoprotein; IV = intravenous; LD = loading dose; PCI = percutaneous coronary intervention; pre angio = before angiography; UA/NSTEMI = unstable angina/non–ST-elevation myocardial infarction; UFH = unfractionated heparin.

   a. Continue ASA. *(Level of Evidence: A)*
   b. Discontinue clopidogrel 5 to 7 d before elective CABG. *(Level of Evidence: B)* More urgent surgery, if necessary, may be performed by experienced surgeons if the incremental bleeding risk is considered acceptable. *(Level of Evidence: C)*
   c. Discontinue intravenous GP IIb/IIIa inhibitor (eptifibatide or tirofiban) 4 h before CABG. *(Level of Evidence: B)*
   d. Anticoagulant therapy should be managed as follows:
      1. Continue UFH. *(Level of Evidence: B)*
      2. Discontinue enoxaparin* 12 to 24 h before CABG and dose with UFH per institutional practice. *(Level of Evidence: B)*
      3. Discontinue fondaparinux 24 h before CABG and dose with UFH per institutional practice. *(Level of Evidence: B)*
      4. Discontinue bivalirudin 3 h before CABG and dose with UFH per institutional practice. *(Level of Evidence: B)*

3. For UA/NSTEMI patients in whom PCI has been selected as a postangiography management strategy, the instructions noted below should be followed (Fig. 9; Box H):
   a. Continue ASA. *(Level of Evidence: A)*
   b. Administer a loading dose of clopidogrel† if not started before diagnostic angiography. *(Level of Evidence: A)*
   c. Administer an intravenous GP IIb/IIIa inhibitor (abciximab, eptifibatide, or tirofiban) if not started before diagnostic angiography for troponin-positive and other high-risk patients *(Level of Evidence: A)*. See Class IIa recommendation below if bivalirudin was selected as the anticoagulant.
   d. Discontinue anticoagulant therapy after PCI for uncomplicated cases. *(Level of Evidence: B)*

4. For UA/NSTEMI patients in whom medical therapy is selected as a postangiography management strategy and in whom no significant obstructive CAD on angiography was found, antiplatelet and anticoagulant therapy should be administered at the discretion of the clinician. *(Level of Evidence: C)* For patients in whom evidence of coronary atherosclerosis is present (e.g., luminal irregularities or intravascular ultrasound-demonstrated lesions), albeit without flow-limiting stenoses, long-term treatment with ASA and other secondary prevention measures should be prescribed. (Fig. 9; Box I) *(Level of Evidence: C)*
5. For UA/NSTEMI patients in whom medical therapy is selected as a postangiography management strategy and in whom CAD was found on angiography, the following approach is recommended (Fig. 9; Box J):
   a. Continue ASA. *(Level of Evidence: A)*
   b. Administer a loading dose of clopidogrel† if not given before diagnostic angiography. *(Level of Evidence: A)*
   c. Discontinue intravenous GP IIb/IIIa inhibitor if started previously. *(Level of Evidence: B)*
   d. Anticoagulant therapy should be managed as follows:
      1. Continue intravenous UFH for at least 48 h or until discharge if given before diagnostic angiography. *(Level of Evidence: A)*

*Limited data are available for the use of other LMWHs (e.g., dalteparin; see Tables 13 and 17) in UA/NSTEMI.

†Some uncertainty exists about optimum dosing of clopidogrel. Randomized trials establishing its efficacy and providing data on bleeding risks used a loading dose of 300 mg orally followed by a daily oral maintenance dose of 75 mg. Higher oral loading doses such as 600 or 900 mg of clopidogrel more rapidly inhibit platelet aggregation and achieve a higher absolute level of inhibition of platelet aggregation, but the additive clinical efficacy and the safety of higher oral loading doses have not been rigorously established.

2. Continue enoxaparin for duration of hospitalization, up to 8 d, if given before diagnostic angiography. *(Level of Evidence: A)*
3. Continue fondaparinux for duration of hospitalization, up to 8 d, if given before diagnostic angiography. *(Level of Evidence: B)*
4. Either discontinue bivalirudin or continue at a dose of 0.25 mg per kg per h for up to 72 h at the physician's discretion, if given before diagnostic angiography. *(Level of Evidence: B)*

6. For UA/NSTEMI patients in whom a conservative strategy is selected and who do not undergo angiography or stress testing, the instructions noted below should be followed (Fig. 8; Box K):
   a. Continue ASA indefinitely. *(Level of Evidence: A)*
   b. Continue clopidogrel for at least 1 month *(Level of Evidence: A)* and ideally up to 1 year. *(Level of Evidence: B)*
   c. Discontinue IV GP IIb/IIIa inhibitor if started previously. *(Level of Evidence: A)*
   d. Continue UFH for 48 h or administer enoxaparin or fondaparinux for the duration of hospitalization, up to 8 d, and then discontinue anticoagulant therapy. *(Level of Evidence: A)*

7. For UA/NSTEMI patients in whom an initial conservative strategy is selected and in whom no subsequent features appear that would necessitate diagnostic angiography (recurrent symptoms/ischemia, HF, or serious arrhythmias), LVEF should be measured. *(Level of Evidence: B)* (Fig. 8; Box L)

CLASS IIa

1. For UA/NSTEMI patients in whom PCI is selected as a postangiography management strategy, it is reasonable to omit administration of an intravenous GP IIb/IIIa antagonist if bivalirudin was selected as the anticoagulant and at least 300 mg of clopidogrel was administered at least 6 h earlier. *(Level of Evidence: B)* (Fig. 9)
2. If LVEF is less than or equal to 0.40, it is reasonable to perform diagnostic angiography. *(Level of Evidence: B)* (Fig. 8; Box M)
3. If LVEF is greater than 0.40, it is reasonable to perform a stress test. *(Level of Evidence: B)* (Fig. 8; Box N)

CLASS IIb

For UA/NSTEMI patients in whom PCI is selected as a postangiography management strategy, it may be reasonable to omit an intravenous GP IIb/IIIa inhibitor if not started before diagnostic angiography for troponin-negative patients without other clinical or angiographic high-risk features. *(Level of Evidence: C)*

CLASS III

Intravenous fibrinolytic therapy is not indicated in patients without acute ST-segment elevation, a true posterior MI, or a presumed new left bundle-branch block. *(Level of Evidence: A)*

Antithrombotic therapy is essential to modify the disease process and its progression to death, MI, or recurrent MI in the majority of patients who have ACS due to thrombosis on a plaque. A combination of ASA, an anticoagulant, and additional antiplatelet therapy represents the most effective therapy. The intensity of treatment is tailored to individual risk, and triple-antithrombotic treatment is used in patients with continuing ischemia or with other high-risk features and in patients oriented to an early invasive strategy (Table 11; Figs. 7, 8, and 9). Table 13 shows the recommended doses of the various agents. A problematic group of patients are those who present with UA/NSTEMI but who are therapeutically anticoagulated with warfarin. In such patients, clinical judgment is needed with respect to initiation of the antiplatelet and anticoagulant therapy recommended in this section. A general guide is not to initiate anticoagulant therapy until the international normalized ratio (INR) is less than 2.0. However, antiplatelet therapy should be initiated even in patients therapeutically anticoagulated with warfarin, especially if an invasive strategy is planned and implantation of a stent is anticipated. In situations where the INR is supratherapeutic, the bleeding risk is unacceptably high, or urgent surgical treatment is necessary, reversal of the anticoagulant effect of warfarin may be considered with either vitamin K or fresh-frozen plasma as deemed clinically appropriate on the basis of physician judgment.

3.2.4. Antiplatelet Agents and Trials (Aspirin, Ticlopidine, Clopidogrel)

3.2.4.1. ASPIRIN

Some of the strongest evidence available about the long-term prognostic effects of therapy in patients with coronary disease pertains to ASA (363). By irreversibly inhibiting COX-1 within platelets, ASA prevents the formation of thromboxane A2, thereby diminishing platelet aggregation promoted by this pathway but not by others. This platelet inhibition is the plausible mechanism for the clinical benefit of ASA, both because it is fully present with low doses of ASA and because platelets represent one of the principal participants in thrombus formation after plaque disruption. Alternative or additional mechanisms of action for ASA are possible, such as an anti-inflammatory effect (364), but they are unlikely to be important at the low doses of ASA that are effective in UA/NSTEMI. Among all clinical investigations with ASA, trials in UA/NSTEMI have consistently documented a striking benefit of ASA compared with placebo independent of the differences in study design, such as time of entry after the acute phase, duration of follow-up, and dose used (365–368) (Fig. 10).

No trial has directly compared the efficacy of different doses of ASA in patients who present with UA/NSTEMI; however, information can be gleaned from a collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, MI, and stroke in high-risk patients (i.e., acute or previous vascular disease or other predisposing conditions) (375). This collaborative meta-analysis pooled data from 195 trials involving more than 143,000 patients and demonstrated a 22% reduction in the odds of vascular death, MI, or stroke with antiplatelet therapy across a broad spectrum of clinical presentations that included patients presenting with UA/NSTEMI. Indirect comparisons of the proportional effects of different doses of ASA ranging from less than 75 mg to up to 1500 mg daily showed similar reductions in the odds of vascular events with doses between 75 and 1500 mg daily; when less than 75 mg was administered daily, the proportional benefit of ASA was reduced by at least one half compared with the higher doses. An analysis from the CURE trial suggested that there was no difference in the rate of thrombotic events according to ASA dose, but there was a dose-dependent increase in bleeding in

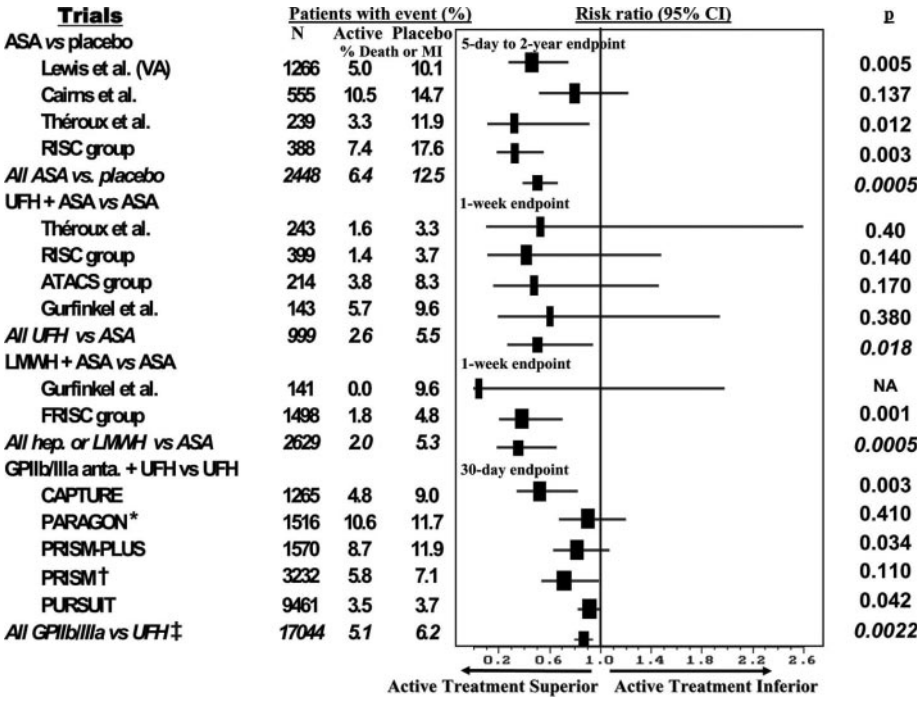


Figure 10. Older Trials of Antiplatelet and Anticoagulant Therapy in UA/NSTEMI

*Best results group. †GPIIb/IIIa with no heparin. ‡All trials except PRISM compared GP IIb-IIIa with UFH versus UFH. Meta-analysis of randomized trials in UA/NSTEMI that have compared ASA with placebo, the combination of UFH and ASA with ASA alone, the combination of an LMWH and ASA with ASA alone, and the combination of a platelet GP IIb/IIIa antagonist, UFH, and ASA with UFH plus ASA. The risk ratio values, 95% CIs, and probability value for each trial are shown. The timing of the end point (death or MI) varied. Results with the platelet GP IIb/IIIa antagonists are reported at the 30-d time point. Incremental gain is observed from single therapy with ASA to double therapy with ASA and UFH and to triple antithrombotic therapy with ASA, UFH, and a platelet GP IIb/IIIa antagonist. In the CAPTURE trial, nearly all patients underwent PCI after 20 to 24 h per study design. Data are taken from PURSUIT (128), PRISM-PLUS (130), Lewis et al. (365), Cairns et al. (366), Théroux et al. (367), RISC group (368), ATACS group (369), Gurfinkel et al. (370), FRISC group (371), CAPTURE (372), PARAGON (373), and PRISM (374). anta. = antagonist; ASA = aspirin; ATACS = Antithrombotic Therapy in Acute Coronary Syndromes; CAPTURE = c7E3 Fab AntiPlatelet Therapy in Unstable REfractory angina; CI = confidence interval; FRISC = FRagmin during InStability in Coronary artery disease; GP = glycoprotein; hep. = heparin; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NA = not applicable; PARAGON = Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network; PCI = percutaneous coronary intervention; PRISM = Platelet Receptor Inhibition in ischemic Syndrome Management; PRISM-PLUS = Platelet Receptor Inhibition in ischemic Syndrome Management in Patients Limited by Unstable Signs and symptoms; PURSUIT = Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy; RISC = Research on InStability in Coronary artery disease; UA/NSTEMI = unstable angina/non–ST-elevation myocardial infarction; UFH = unfractionated heparin; VA = Veterans Affairs.

patients receiving ASA (plus placebo): the major bleeding rate was 2.0% in patients taking less than 100 mg of ASA, 2.3% with 100 to 200 mg, and 4.0% with greater than 200 mg per d (243,376). Therefore, maintenance doses of 75 to 162 mg of ASA are preferred.

The prompt action of ASA and its ability to reduce mortality rates in patients with suspected MI enrolled in the Second International Study of Infarct Survival (ISIS-2) trial led to the recommendation that ASA be initiated immediately in the ED once the diagnosis of ACS is made or suspected. Aspirin therapy also can be started in the prehospital setting when ACS is suspected. On the basis of prior randomized trial protocols and clinical experience, the initial dose of ASA should be between 162 and 325 mg. Although some trials have used enteric-coated ASA for initial dosing, more rapid buccal absorption occurs with non–enteric-coated formulations (377). After stenting, a higher initial maintenance dose of ASA of 325 mg per d has been recommended for 1 month after bare-metal stent implantation and 3 to 6 months after drug-eluting stent (DES) implantation (2). This was based primarily on clinical trials that led to approval of these stents, which used the higher doses initially. However, a dosage change to a range of 162 to 325 mg per d initially has been subsequently recommended, based on risk of excess bleeding and an update of current evidence for ASA dosing (Table 13; Fig. 11).

In patients who are already receiving ASA, it should be continued. The protective effect of ASA has been sustained for at least 1 to 2 years in clinical trials in UA/NSTEMI. Longer term follow-up data in this population are lacking. Long-term efficacy can be extrapolated from other studies of ASA therapy in CAD. Studies in patients with prior MI, stroke, or transient ischemic attack have shown statistically significant benefit during the first 2 years and some additional but not statistically significant benefit during the third year (363). In the absence of large comparison trials of different durations of antiplatelet treatment in patients with CVD or in primary prevention, it seems prudent to continue ASA indefinitely unless side effects are present (1,4,365). Thus, patients should be informed of the evidence that

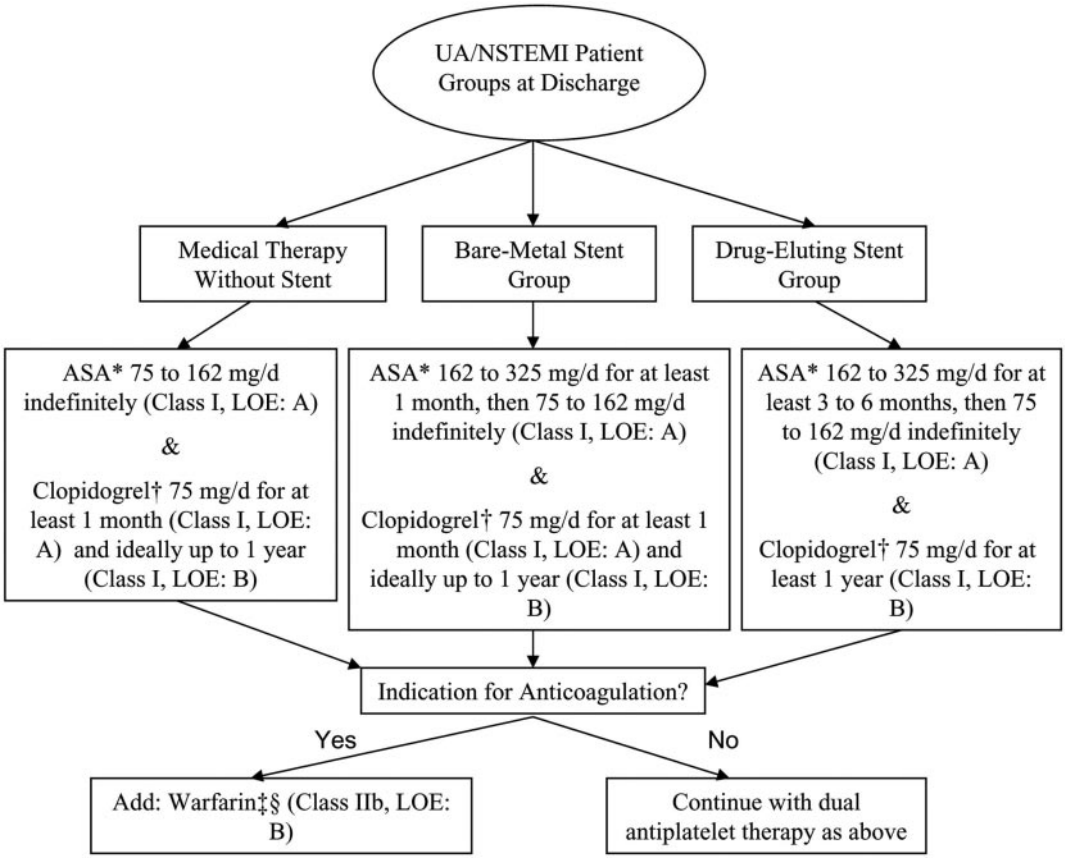


Figure 11. Long-Term Anticoagulant Therapy at Hospital Discharge After UA/NSTEMI

*For aspirin (ASA) allergic patients, use clopidogrel alone (indefinitely), or try aspirin desensitization. †For clopidogrel allergic patients, use ticlopidine, 250 mg by mouth twice daily. ‡Continue ASA indefinitely and warfarin longer term as indicated for specific conditions such as atrial fibrillation; LV thrombus; cerebral, venous, or pulmonary emboli. §When warfarin is added to aspirin plus clopidogrel, an INR of 2.0 to 2.5 is recommended. INR = international normalized ratio; LOE = level of evidence; LV = left ventricular; UA/NSTEMI = unstable angina/non–ST-elevated myocardial infarction.

supports the use of ASA in UA/NSTEMI and CAD in general and instructed to continue the drug indefinitely, unless a contraindication develops. It is important to emphasize to patients that there is a sound rationale for concomitant use of ASA even if other antithrombotic drugs, such as clopidogrel or warfarin, are administered concurrently (Fig. 11) and that withdrawal or discontinuation of ASA or clopidogrel has been associated with recurrent episodes of ACS, including stent thrombosis (378–380). Finally, because of a drug interaction between ibuprofen and ASA, patients should be advised to use an alternative NSAID or to take their ibuprofen dose at least 30 min after ingestion of immediate-release ASA or at least 8 h before ASA ingestion to avoid any potential diminution of the protective effects of ASA. No recommendations about the concomitant use of ibuprofen and enteric-coated low-dose ASA can be made on the basis of available data (381).

Contraindications to ASA include intolerance and allergy (primarily manifested as asthma with nasal polyps), active bleeding, hemophilia, active retinal bleeding, severe untreated hypertension, an active peptic ulcer, or another serious source of gastrointestinal or genitourinary bleeding. Gastrointestinal side effects such as dyspepsia and nausea are infrequent with the low doses. Primary prevention trials have reported a small excess in intracranial bleeding, which is offset in secondary prevention trials by the prevention of ischemic stroke. It has been proposed that there is a negative interaction between ACE inhibitors and ASA, with a reduction in the vasodilatory effects of ACE inhibitors, presumably because ASA inhibits ACE inhibitor–induced prostaglandin synthesis. This interaction does not appear to interfere importantly with the clinical benefits of therapy with either agent (382). Therefore, unless there are specific contraindications, ASA should be administered to all patients with UA/NSTEMI.

3.2.4.2. ADENOSINE DIPHOSPHATE RECEPTOR ANTAGONISTS AND OTHER ANTIPLATELET AGENTS

Two thienopyridines—ticlopidine and clopidogrel—are ADP receptor (P2Y12) antagonists that are approved for antiplatelet therapy (383). The platelet effects of ticlopidine and clopidogrel are irreversible but take several days to achieve

maximal effect in the absence of a loading dose. The administration of a loading dose can shorten the time to achievement of effective levels of antiplatelet therapy. Because the mechanisms of the antiplatelet effects of ASA and ADP antagonists differ, a potential exists for additive benefit with the combination. In patients with a history of gastrointestinal bleeding, when ASA or a thienopyridine is administered alone or in combination, drugs to minimize the risk of recurrent gastrointestinal bleeding (e.g., proton-pump inhibitors) should be prescribed concomitantly (384–386).

Ticlopidine has been used successfully for the secondary prevention of stroke and MI and for the prevention of stent closure and graft occlusion (387). The adverse effects of ticlopidine limit its usefulness: gastrointestinal problems (diarrhea, abdominal pain, nausea, and vomiting), neutropenia in approximately 2.4% of patients, severe neutropenia in 0.8% of patients, and, rarely, thrombotic thrombocytopenia purpura (388). Neutropenia usually resolves within 1 to 3 weeks of discontinuation of therapy but very rarely may be fatal. Thrombotic thrombocytopenia purpura, which is a very uncommon, life-threatening complication, requires immediate plasma exchange. Monitoring of ticlopidine therapy requires a complete blood count that includes a differential count every 2 weeks for the first 3 months of therapy.

Extensive clinical experience with clopidogrel is derived in part from the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial (389). A total of 19,185 patients were randomized to receive ASA 325 mg per d or clopidogrel 75 mg per d. Entry criteria consisted of atherosclerotic vascular disease manifested as recent ischemic stroke, recent MI, or symptomatic peripheral arterial disease. Follow-up extended for 1 to 3 years. The RR of ischemic stroke, MI, or vascular death was reduced by 8.7% in favor of clopidogrel from 5.8% to 5.3% ($p = 0.04$). The benefit was greatest for patients with peripheral arterial disease. This group had a 24% relative risk reduction ($p = 0.03$). There was a slightly increased, but minimal, incidence of rash and diarrhea with clopidogrel treatment and slightly more bleeding with ASA. There was no excess neutropenia with clopidogrel, which contrasts with ticlopidine. The results provide evidence that clopidogrel is at least as effective as ASA and appears to be modestly more effective. In 1 report, 11 severe cases of thrombotic thrombocytopenia purpura were described as occurring within 14 d after the initiation of clopidogrel; plasma exchange was required in 10 of the patients, and 1 patient died (390). These cases occurred among more than 3 million patients treated with clopidogrel.

Clopidogrel is reasonable antiplatelet therapy for secondary prevention, with an efficacy at least similar to that of ASA. Clopidogrel is indicated in patients with UA/NSTEMI who are unable to tolerate ASA due to either hypersensitivity or major gastrointestinal contraindications, principally recent significant bleeding from a peptic ulcer or gastritis. In patients with a history of gastrointestinal bleeding while taking ASA, when a thienopyridine is administered, drugs to minimize the risk of recurrent gastrointestinal bleeding (e.g., proton-pump inhibitors) should be prescribed concomitantly (384–386). When treatment with thienopyridines is considered during the acute phase, it should be recognized that there is a delay before attainment of the full antiplatelet effect. Clopidogrel is preferred to ticlopidine because it more rapidly inhibits platelets and appears to have a more favorable safety profile.

An oral loading dose (300 mg) of clopidogrel is typically used to achieve more rapid platelet inhibition. The optimal loading dose with clopidogrel has not been rigorously established. The greatest amount of general clinical experience and randomized trial data exist for a clopidogrel loading dose of 300 mg, which is the approved loading dose. Higher loading doses (600 to 900 mg) have been evaluated (391,392). They appear to be safe and more rapidly acting; however, it must be recognized that the database for such higher loading doses is not sufficiently robust to formulate definitive recommendations. Most studies to date with higher loading doses of clopidogrel have examined surrogates for clinical outcomes, such as measurements of 1 or more markers of platelet aggregation or function. When groups of patients are studied, a general dose response is observed with increasing magnitude and speed of onset of inhibition of platelet aggregation in response to agonists such as ADP as the loading dose increases. However, considerable interindividual variation in antiplatelet effect also is observed with all loading doses of clopidogrel, which makes it difficult to predict the impact of different loading doses of clopidogrel in a specific patient. Small to moderate-sized trials have reported favorable outcomes with a 600-mg versus a 300-mg loading dose in patients undergoing PCI (393); however, large-scale randomized trials are still needed to definitively compare the efficacy and safety of different loading regimens of clopidogrel. This is of particular importance because it is known that patients undergoing CABG surgery shortly after receiving 300 mg of clopidogrel have an increased risk of bleeding (394); the relative risk of bleeding associated with higher loading doses of clopidogrel remains to be established. The Writing Committee endorses the performance of appropriately designed clinical trials to identify the optimal loading dose of clopidogrel.

Two randomized trials compared clopidogrel with ticlopidine. In 1 study, 700 patients who successfully received a stent were randomized to receive 500 mg of ticlopidine or 75 mg of clopidogrel, in addition to 100 mg of ASA, for 4 weeks (395). Cardiac death, urgent target-vessel revascularization, angiographically documented thrombotic stent occlusion, or nonfatal MI within 30 d occurred in 3.1% of patients who received clopidogrel and 1.7% of patients who received ticlopidine ($p = 0.24$), and noncardiac death, stroke, severe peripheral vascular hemorrhagic events, or any adverse event that resulted in the discontinuation of the study medication occurred in 4.5% and 9.6% of patients, respectively ($p = 0.01$). The CLopidogrel ASpirin Stent

International Cooperative Study (CLASSICS) (396) was conducted in 1,020 patients. A loading dose of 300 mg of clopidogrel followed by 75 mg per d was compared to a daily dose of 75 mg without a loading dose and with a loading dose of 150 mg of ticlopidine followed by 150 mg twice per day (patients in each of the 3 arms also received ASA). The first dose was administered 1 to 6 h after stent implantation; the treatment duration was 28 d. The trial showed better tolerance to clopidogrel with or without a loading dose than to ticlopidine. Stent thrombosis or major complications occurred at the same frequency in the 3 groups.

The CURE trial randomized 12,562 patients with UA and NSTEMI presenting within 24 h to placebo or clopidogrel (loading dose of 300 mg followed by 75 mg daily) and followed them for 3 to 12 months (243). All patients received ASA. Cardiovascular death, MI, or stroke occurred in 11.5% of patients assigned to placebo and 9.3% assigned to clopidogrel (RR = 0.80, p less than 0.001). In addition, clopidogrel was associated with significant reductions in the rate of in-hospital severe ischemia and revascularization, as well as the need for fibrinolytic therapy or intravenous GP IIb/IIIa receptor antagonists. These results were observed across a wide variety of subgroups. A reduction in recurrent ischemia was noted within the first few hours after randomization.

There was an excess of major bleeding (2.7% in the placebo group vs. 3.7% in the clopidogrel group, $p = 0.003$) and of minor bleeding but not of life-threatening bleeding. The risk of bleeding was increased in patients undergoing CABG surgery within the first 5 d of stopping clopidogrel. The CURE study was conducted at centers in which there was no routine policy regarding early invasive procedures; revascularization was performed during the initial admission in only 23% of the patients. Although the addition of a platelet GP IIb/IIIa inhibitor in patients receiving ASA, clopidogrel, and heparin in CURE was well tolerated, fewer than 10% of patients received this combination. Therefore, additional information on the safety of an anticoagulant and a GP IIb/IIIa inhibitor in patients already receiving ASA and clopidogrel should be obtained. Accurate estimates of the treatment benefit of clopidogrel in patients who received GP IIb/IIIa antagonists remain ill-defined.

The CURE trial also provides strong evidence for the addition of clopidogrel to ASA on admission in the management of patients with UA and NSTEMI in whom a noninterventional approach is intended, an especially useful approach in hospitals that do not have a routine policy about early invasive procedures. The event curves for the 2 groups separate early. The optimal duration of therapy with clopidogrel in patients who have been managed exclusively medically has not been determined, but the favorable results in CURE were observed over a period averaging 9 months and for up to 1 year.

The PCI-CURE study was an observational substudy of the patients undergoing PCI within the larger CURE trial (397). In the PCI-CURE study, 2,658 patients had previously been randomly assigned to double-blind treatment with clopidogrel (n = 1313) as per the CURE protocol or placebo (n = 1,345). Patients were pretreated with ASA and the study drug for a median of 10 d. After PCI, most patients received open-label thienopyridine for approximately 4 weeks, after which the blinded study drug was restarted for a mean of 8 months. Fifty-nine patients (4.5%) in the clopidogrel group had the primary end point (a composite of cardiovascular death, MI, or urgent target-vessel revascularization) within 30 d of PCI compared with 86 (6.4%) in the placebo group (RR = 0.70, 95% CI 0.50 to 0.97, $p = 0.03$). Overall, including events before and after PCI, there was a 31% reduction in cardiovascular death or MI ($p = 0.002$). Thus, in patients with UA and NSTEMI receiving ASA and undergoing PCI, a strategy of clopidogrel pretreatment followed by up to 1 year of clopidogrel use (and probably at least 1 year in those with DES; see below) is beneficial in reducing major cardiovascular events compared with placebo and appears to be cost-effective (the incremental cost-effectiveness ratio for clopidogrel plus ASA compared with ASA alone was $15,400 per quality-adjusted life-year) (398). Therefore, clopidogrel should be used routinely in patients who undergo PCI.

Pathological and clinical evidence particularly highlights the need for longer-term ADP-receptor blockade in patients who receive DES (399). DESs consistently have been shown to reduce stent restenosis. However, this same antiproliferative action can delay endothelialization, predisposing to stent thrombosis including late (beyond 3–6 months) or very late (after 1 year) thrombosis after stent placement (399,399a,400). These concerns have raised questions about the ideal duration of dual antiplatelet therapy (DAT) and the overall balance of benefit/risk of DES compared with bare-metal stents (401). A number of comparisons of outcomes up to 4 years after DES and bare-metal stent implantation, including the initial FDA approval trials, have been published (400,402–404,404a–404f). These confirm a marked reduction in restenosis and consequent repeat revascularization procedures with DES (404c). However, although results have varied, they also suggest a small incremental risk (of about 0.5%) of stent thrombosis (404a–404c). Reassuringly, they have not shown an overall increase in death or MI after DES versus bare-metal stents, suggesting offsetting advantages of improved revascularization versus increased stent thrombosis risk. These observations also emphasize the need for a continued search for more biocompatible stents that minimize restenosis without increasing the risks of thrombosis.

In the ISAR-REACT-2 trial, patients undergoing PCI were assigned to receive either abciximab (bolus of 0.25 mg per kg of body weight, followed by a 0.125-mg per kg per min [maximum, 10 mg per min] infusion for 12 h, plus heparin 70 U per kg of body weight) or placebo (placebo bolus and infusion of 12 h, plus heparin bolus, 140 U per kg) (244). All patients received 600 mg of clopidogrel at least 2 h before the procedure, as well as 500 mg of oral or intravenous ASA. Of 2,022 patients enrolled, 1,012 were

assigned to abciximab and 1,010 to placebo. The primary end point was reached in 90 patients (8.9%) assigned to abciximab versus 120 patients (11.9%) assigned to placebo, a 25% reduction in risk with abciximab (RR = 0.75, 95% CI 0.58 to 0.97, $p = 0.03$) (244). Among patients without an elevated cTn level, there was no difference in the incidence of primary end-point events between the abciximab group (23 [4.6%] of 499 patients) and the placebo group (22 [4.6%] of 474 patients; RR = 0.99, 95% CI 0.56 to 1.76, $p = 0.98$), whereas among patients with an elevated cTn level, the incidence of events was significantly lower in the abciximab group (67 [13.1%] of 513 patients) than in the placebo group (98 [18.3%] of 536 patients), which corresponds to an RR of 0.71 (95% CI 0.54 to 0.95, $p = 0.02$; $p = 0.07$ for interaction). There were no significant differences between the 2 groups with regard to the risk of major or minor bleeding or the need for transfusion. Thus, it appears beneficial to add an intravenous GP IIb/IIIa inhibitor to thienopyridine treatment if an invasive strategy is planned in patients with high-risk features (e.g., elevated cTn level; Figs. 7, 8, and 9).

The optimal timing of administration of the loading dose of clopidogrel for those who are managed with an early invasive strategy cannot be determined with certainty from PCI-CURE because there was no comparison of administration of the loading dose before diagnostic angiography ("upstream treatment") versus at the time of PCI ("in-lab treatment"). However, based on the early separation of the curves, when there is delay to coronary angiography, patients should receive clopidogrel as initial therapy (Figs. 7, 8, and 9). The Clopidogrel for the Reduction of Events During Observation (CREDO) trial (405), albeit not designed specifically to study UA/NSTEMI patients, provides partially relevant information on the question of timing of the loading dose. Patients with symptomatic CAD and evidence of ischemia who were referred for PCI and those who were thought to be highly likely to require PCI were randomized to receive clopidogrel (300 mg) or matching placebo 3 to 24 h before PCI. All subjects received a maintenance dose of clopidogrel (75 mg daily) for 28 d. Thus, CREDO is really a comparison of the administration of a loading dose before PCI versus not administering a loading dose at all. There is no explicit comparison within CREDO of a pre-PCI loading dose versus a loading dose in the catheterization laboratory. In CREDO, the relative risk for the composite end point of death/MI/urgent target-vessel revascularization was 0.82, in favor of the group who received a loading dose before PCI compared with the opposite arm that did not receive a loading dose, but this did not reach statistical significance ($p = 0.23$). Subgroup analyses within CREDO suggest that if the loading dose is given at least 6 or preferably 15 h before PCI, fewer events occur compared with no loading dose being administered (406). One study from the Netherlands that compared pretreatment with clopidogrel before PCI versus administration of a loading dose at the time of PCI in patients undergoing elective PCI showed no difference in biomarker release or clinical end points (407).

Thus, there now appears to be an important role for clopidogrel in patients with UA/NSTEMI, both in those who are managed conservatively and in those who undergo PCI, especially stenting, or who ultimately undergo CABG surgery (408). However, it is not entirely clear how long therapy should be maintained (409,410). Whereas increased hazard is clearly associated with premature discontinuation of dual antiplatelet therapy after DES (405,411,412), the benefit of extended therapy beyond 1 year is uncertain (401,403d,403e). Hence, the minimum requirements for DAT duration should be vigorously applied for each DES type. However, 1 year of DAT may be ideal for all UA/NSTEMI patients who are not at high risk of bleeding given the secondary preventive effects of DAT, perhaps especially after DES. On the other hand, the limited database at this point in time does not support a recommendation for DAT beyond 1 year for all DES-treated patients (401,403d,403e). For patients with clinical features associated with an increased risk of stent thrombosis, such as diabetes or renal insufficiency or procedural characteristics such as multiple stents or a treated bifurcation lesion, extended DAT may be reasonable. Data on the relative merits of DES versus bare-metal stents in "off-label" patients (such as multivessel disease or MI), who are at higher risk and experience higher event rates, and of the ideal duration of DAT in these patients, are limited and are currently insufficient to draw separate conclusions (401,403d,403e).

Because of the importance of dual-antiplatelet therapy with ASA and a thienopyridine after implantation of a stent, especially if a DES is being considered, clinicians should ascertain whether the patient can comply with 1 year of dual-antiplatelet therapy. Patients should also be instructed to contact their treating cardiologist before stopping any antiplatelet therapy, because abrupt discontinuation of antiplatelet therapy can put the patient at risk of stent thrombosis, an event that may result in MI or even death (411). Health care providers should postpone elective surgical procedures until beyond 12 months after DES implantation (411). If a surgical procedure must be performed sooner than 12 months, an effort should be made to maintain the patient on ASA and minimize the period of time of discontinuation of a thienopyridine (411).

In the CURE study, which predominantly involved medical management of patients with UA/NSTEMI, the relative risk reduction in events was of a similar magnitude (approximately 20%) during the first 30 d after randomization as during the ensuing cumulative 8 months (413). In contrast, clopidogrel was not beneficial in a large trial of high-risk primary prevention patients (414).

Because clopidogrel, when added to ASA, increases the risk of bleeding during major surgery, it has been recommended that clopidogrel be withheld for at least 5 d (243) and up to 7 d before surgery in patients who are scheduled for elective CABG (376,415). In many hospitals in which

patients with UA/NSTEMI undergo rapid diagnostic catheterization within 24 h of admission, clopidogrel is not started until it is clear that CABG will not be scheduled within the next several days. However, unstable patients should receive clopidogrel or be taken for immediate angiography (Figs. 7, 8, and 9). A loading dose of clopidogrel can be given to a patient on the catheterization table if a PCI is to be performed immediately. If PCI is not performed, clopidogrel can be given after the catheterization. However, when clopidogrel is given before catheterization and urgent surgical intervention is indicated, some experience suggests that "early" bypass surgery may be undertaken by experienced surgeons at acceptable incremental bleeding risk. Among 2,858 UA/NSTEMI patients in the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) Registry undergoing CABG, 30% received acute clopidogrel therapy, the majority of these (87%) within 5 d of surgery. "Early" CABG after clopidogrel was associated with a significant increase in any blood transfusion (OR 1.36, 95% CI 1.10 to 1.68) and the need for 4 or more units of blood (OR 1.70, 95% CI 1.32 to 2.1). In-hospital rates of death were low (3% to 4%), and no difference was noted in rates of death, reinfarction, or stroke with "early" CABG in patients treated with versus without acute clopidogrel (394). The Writing Committee believes that more data on the overall relative benefits versus risks of proceeding with early bypass surgery in the presence of clopidogrel therapy are desirable and necessary in order to formulate better-informed recommendations for the timing of surgery in the UA/NSTEMI patient.

Sulfinpyrazone, dipyridamole, prostacyclin, and prostacyclin analogs have not been demonstrated to be of benefit in UA or NSTEMI and are not recommended. The thromboxane synthase blockers and thromboxane A2 receptor antagonists have been evaluated in ACS and have not shown any advantage over ASA. A number of other antiplatelet drugs are currently available, and still others are under active investigation. Clopidogrel is currently the preferred thienopyridine because of its extensive evidence base, its more rapid onset of action, especially after a loading dose (417,418), and its better safety profile than ticlopidine (396).

Evidence has emerged that there is considerable interpatient variability in the response to clopidogrel, with a wide range of inhibition of platelet aggregation after a given dose (419). Patients with diminished responsiveness to clopidogrel appear to be at increased risk of ischemic events (420,421). The reasons for the large interpatient variability in responsiveness to clopidogrel are under investigation, but variation in absorption, generation of the active metabolite, and drug interactions are leading possibilities. Maneuvers to overcome poor responsiveness to clopidogrel may involve an increase in the dose (422). However, techniques for monitoring for poor response to clopidogrel and the appropriate dosing strategy when it is uncovered remain to be established.

3.2.5. Anticoagulant Agents and Trials

A number of drugs are available to clinicians for management of patients with UA/NSTEMI. Although the medical literature sometimes refers to such drugs as "antithrombins," the Writing Committee has chosen to refer to them as anticoagulants because they often inhibit 1 or more proteins in the coagulation cascade before thrombin. Evaluation of anticoagulant strategies is an active area of investigation. It is difficult to draw conclusions that 1 anticoagulant strategy is to be preferred over another given the uncertainty of whether equipotent doses were administered, the different durations of treatment studied across the trials, and the fact that many patients were already receiving 1 open-label anticoagulant before they were randomized in a trial to another anticoagulant (which makes it uncertain what residual effect the open-label anticoagulant had in the trial). Other aspects of the data set that confound interpretation of the impact of specific anticoagulant strategies include a range of antiplatelet strategies administered concomitantly with the anticoagulant and the addition of a second anticoagulant, either because of clinician preference or as part of protocol design (423–425) as patients moved from the medical management phase to the interventional management phase of treatment for UA/NSTEMI.

The Writing Committee also wishes to draw attention to the fact that active-control noninferiority trials are being performed with increasing frequency as it becomes ethically increasingly difficult to perform placebo-controlled trials. In this update, for example, noninferiority ("equivalence") comparisons on primary or major secondary end points were important in the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) (425), Organization to Assess Strategies for Ischaemic Syndromes (OASIS-5) (424), and Randomized Evaluation of PCI Linking Angiomax to reduced Clinical Events (REPLACE-2) (426) studies. Although practically useful, noninferiority analyses depend on assumptions not inherent in classic superiority analytical designs and thus present additional limitations and interpretative challenges (427–429). Noninferiority trials require an a priori choice of a "noninferiority margin," typically defined in terms of a fraction of standard treatment effect to be preserved compared with a putative placebo (e.g., 0.5) and which rests on clinical judgment and statistical issues (428). Because noninferiority trials do not have a placebo control, these assumptions cannot be easily verified. Thus, whether the new therapy indeed is therapeutically "equivalent" is less certain than in a superiority trial. Hence, additional caution in weighing and applying the results of noninferiority trials is appropriate.

The Writing Committee believes that a number of acceptable anticoagulant strategies can be recommended with a Class I status but emphasizes the fact that a preference for a particular strategy is far from clear (Figs. 7,

8, and 9). It is suggested that each institution agree on a consistent approach to minimize the chance of medication errors and double anticoagulation when personal preferences are superimposed on an already-initiated treatment plan. Factors that should be weighed when one considers an anticoagulant strategy (or set of strategies to cover the range of patient scenarios) include established efficacy, risk of bleeding in a given patient, cost, local familiarity with dosing regimens (particularly if PCI is planned), anticipated need for surgery, and the desire to promptly reverse the anticoagulant effect if bleeding occurs.

Unfractionated heparin exerts its anticoagulant effect by accelerating the action of circulating antithrombin, a proteolytic enzyme that inactivates factor IIa (thrombin), factor IXa, and factor Xa. It prevents thrombus propagation but does not lyse existing thrombi (430). Unfractionated heparin is a heterogeneous mixture of polysaccharide chains of molecular weights that range from 5,000 to 30,000 Daltons and have varying effects on anticoagulant activity. Unfractionated heparin binds to a number of plasma proteins, blood cells, and endothelial cells. The LMWHs are obtained through chemical or enzymatic depolymerization of the polysaccharide chains of heparin to provide chains with different molecular weight distributions. Approximately 25% to 50% of the pentasaccharide-containing chains of LMWH preparations contain more than 18 saccharide units, and these are able to inactivate both thrombin and factor Xa. Low-molecular-weight heparin chains that are fewer than 18 saccharide units retain their ability to inactivate factor Xa but not thrombin. Therefore, LMWHs are relatively more potent in facilitating inhibition of factor Xa than in the inactivation of thrombin. Distinct advantages of LMWH over UFH include decreased binding to plasma proteins and endothelial cells and dose-independent clearance, with a longer half-life that results in more predictable and sustained anticoagulation with once- or twice-a-day subcutaneous administration. An advantage of LMWHs is that they do not usually require laboratory monitoring of activity. The pharmacodynamic and pharmacokinetic profiles of the different commercial preparations of LMWHs vary, with their mean molecular weights ranging from 4,200 to 6,000 Daltons. Accordingly, their ratios of anti–factor Xa to anti–factor IIa vary, ranging from 1.9 to 3.8 (431). By contrast, the direct thrombin inhibitors specifically block thrombin without the need for a cofactor. Hirudin binds directly to the anion binding site and the catalytic sites of thrombin to produce potent and predictable anticoagulation (432).

Bivalirudin is a synthetic analog of hirudin that binds reversibly to thrombin and inhibits clot-bound thrombin. More upstream in the coagulation cascade are factor Xa inhibitors, such as the synthetic pentasaccharide fondaparinux, that act proximally to inhibit the multiplier effects of the downstream coagulation reactions and thereby reduce the amount of thrombin that is generated. Advantages of fondaparinux compared with UFH include decreased binding to plasma proteins and endothelial cells and dose-independent clearance, with a longer half-life that results in more predictable and sustained anticoagulation with fixed-dose, once-a-day subcutaneous administration. An advantage of these agents over UFH is that like the LMWHs, fondaparinux does not require laboratory monitoring of activity. Fondaparinux is cleared renally, as is the anti–Xa activity of enoxaparin. The factor Xa inhibitors do not have any action against thrombin that is already formed or that is generated despite their administration, which possibly contributes to the observation of an increased rate of catheter thrombosis when factor Xa inhibitors such as fondaparinux are used alone to support PCI procedures. In the case of both the direct thrombin inhibitors and fondaparinux, it is not possible to reverse the effect with protamine because they lack a protamine-binding domain; reversal of their action in the event of bleeding requires discontinuation of their administration and, if needed, transfusion of coagulation factors (e.g., fresh-frozen plasma).

In summary, whereas anticoagulant therapy forms a basic element of UA/NSTEMI therapy, recommendation of an anticoagulant regimen has become more complicated by a number of new choices suggested by contemporary trials, some of which do not provide adequate comparative information for common practice settings. The Writing Committee believes that inadequate unconfounded comparative information is available to recommend a preferred regimen when an early, invasive strategy is used for UA/NSTEMI, and physician and health care system preference, together with individualized patient application, is advised. Additional experience may change this viewpoint in the future. On the other hand, these available trials are less confounded for the large number of patients treated with an initial noninvasive or delayed invasive strategy: they suggest an anticoagulant preference for these patients treated with a noninvasive strategy in the order of fondaparinux, enoxaparin, and UFH (least preferred), using the specific regimens tested in these trials. Bivalirudin has not been tested in a noninvasive strategy and hence cannot be recommended currently. Even in this group, the order of preference often depends on a single, albeit large, trial, so that additional clinical trial information will be welcomed.

The optimal duration of anticoagulation therapy remains undefined. Evidence for recurrence of events after cessation of short-duration intravenous UFH and results of studies in STEMI patients demonstrating superiority of anticoagulant agents that are administered for the duration of the hospital stay suggest that anticoagulation duration of more than 2 d for those who are managed with a conservative strategy may be beneficial, but this requires further study (433,434).

3.2.5.1. UNFRACTIONATED HEPARIN

Six relatively small randomized, placebo-controlled trials with UFH have been reported (435–440). The results of studies that compared the combination of ASA and heparin

with ASA alone are shown in Figure 10. In the trials that used UFH, the reduction in the rate of death or MI during the first week was 54% ($p = 0.016$), and in the trials that used either UFH or LMWH, the reduction was 63%. Two published meta-analyses have included different studies. In 1 meta-analysis, which involved 3 randomized trials and an early end point (less than 5 d) (369), the risk of death or MI with the combination of ASA and heparin was reduced by 56% ($p = 0.03$). In the second meta-analysis, which involved 6 trials and end points that ranged from 2 to 12 weeks, the RR was reduced by 33% ($p = 0.06$) (441). Most of the benefits of the various anticoagulants are short term, however, and are not maintained on a long-term basis. Reactivation of the disease process after the discontinuation of anticoagulants may contribute to this loss of early gain among medically treated patients that has been described with UFH (442), dalteparin (371), and hirudin (443,444). The combination of UFH and ASA appears to mitigate this reactivation in part (442,445), although there is hematologic evidence of increased thrombin activity after the cessation of intravenous UFH ("rebound") even in the presence of ASA (446). Uncontrolled observations suggested a reduction in the "heparin rebound" by switching from intravenous to subcutaneous UFH for several days before the drug is stopped.

Unfractionated heparin has important pharmacokinetic limitations that are related to its nonspecific binding to proteins and cells. These pharmacokinetic limitations of UFH translate into poor bioavailability, especially at low doses, and marked variability in anticoagulant response among patients (447). As a consequence of these pharmacokinetic limitations, the anticoagulant effect of heparin requires monitoring with the activated partial thromboplastin time (aPTT), a test that is sensitive to the inhibitory effects of UFH on thrombin (factor IIa), factor Xa, and factor IXa. Many clinicians have traditionally prescribed a fixed initial dose of UFH (e.g., 5,000 U bolus, 1,000 U per h initial infusion); clinical trials have indicated that a weight-adjusted dosing regimen can provide more predictable anticoagulation than the fixed-dose regimen (448–450). The weight-adjusted regimen recommended is an initial bolus of 60 U per kg (maximum 4,000 U) and an initial infusion of 12 U per kg per h (maximum 1,000 U per h). The therapeutic range of the various nomograms differs due to variation in the laboratory methods used to determine aPTT. The American College of Chest Physicians consensus conference (451) has therefore recommended dosage adjustments of the nomograms to correspond to a therapeutic range equivalent to heparin levels of 0.3 to 0.7 U per ml by anti–factor Xa determinations, which correlates with aPTT values between 60 and 80 s. In addition to body weight, other clinical factors that affect the response to UFH include age and sex, which are associated with higher aPTT values, and smoking history and diabetes mellitus, which are associated with lower aPTT values (447,452). At high doses, heparin is cleared renally (451).

Even though weight-based UFH dosing regimens are used, the aPTT should be monitored for adjustment of UFH dosing. Because of variation among hospitals in the control aPTT values, nomograms should be established at each institution that are designed to achieve aPTT values in the target range (e.g., for a control aPTT of 30 s, the target range [1.5 to 2.5 times control] would be 45 to 75 s). Delays in laboratory turnaround time for aPPT results also can be a source of variability in care, resulting in over- or under-anticoagulation for prolonged time periods, and should be avoided. Measurements should be made 6 h after any dosage change and used to adjust UFH infusion until the aPTT exhibits a therapeutic level. When 2 consecutive aPTT values are therapeutic, the measurements may be made every 24 h and, if necessary, dose adjustment performed. In addition, a significant change in the patient's clinical condition (e.g., recurrent ischemia, bleeding, or hypotension) should prompt an immediate aPTT determination, followed by dose adjustment, if necessary.

Serial hemoglobin/hematocrit and platelet measurements are recommended at least daily during UFH therapy. In addition, any clinically significant bleeding, recurrent symptoms, or hemodynamic instability should prompt their immediate determination. Serial platelet counts are necessary to monitor for heparin-induced thrombocytopenia. Mild thrombocytopenia may occur in 10% to 20% of patients who are receiving heparin, whereas significant thrombocytopenia (platelet count less than 100,000) occurs in 1% to 5% of patients and typically appears after 4 to 14 d of therapy (453–457). A rare but dangerous complication (less than 0.2% incidence) is autoimmune UFH-induced thrombocytopenia with thrombosis, which can occur both shortly after initiation of UFH or, rarely, in a delayed (i.e., after 5 to 19 d or more), often unrecognized form (458–460). A high clinical suspicion mandates the immediate cessation of all heparin therapy (including that used to flush intravenous lines).

Most of the trials that evaluated the use of UFH in UA/NSTEMI have continued therapy for 2 to 5 d. The optimal duration of therapy remains undefined.

3.2.5.2. LOW-MOLECULAR-WEIGHT HEPARIN

In a pilot open-label study, 219 patients with UA were randomized to receive ASA (200 mg per d), ASA plus UFH, or ASA plus nadroparin (an LMWH) (370). The combination of ASA and LMWH significantly reduced the total ischemic event rate, the rate of recurrent angina, and the number of patients requiring interventional procedures.

The FRISC study (371) randomized 1,506 patients with UA or non–Q-wave MI to receive subcutaneous administration of the LMWH dalteparin (120 IU per kg twice daily) or placebo for 6 d and then once a day for the next 35 to 45 d. Dalteparin was associated with a 63% risk reduction in death or MI during the first 6 d (4.8% vs. 1.8%, $p = 0.001$), which matched the favorable experience observed with UFH. Although an excess of events was observed after

the dose reduction to once daily after 6 d, a significant decrease was observed at 40 d with dalteparin in the composite outcome of death, MI, or revascularization (23.7% vs. 18.0%, $p = 0.005$), and a trend was noted toward a reduction in rates of death or MI (10.7% vs. 8.0%, $p = 0.07$).

Because the level of anticoagulant activity cannot be easily measured in patients receiving LMWH (e.g., aPTT or activated clotting time [ACT]), interventional cardiologists have expressed concern about the substitution of LMWH for UFH in patients scheduled for catheterization with possible PCI. However, in a study involving 293 patients with UA/NSTEMI who received the usual dose of enoxaparin, Collett et al. (461) showed that PCI can be performed safely.

An alternative approach is to use LMWH during the period of initial stabilization. The dose can be withheld on the morning of the procedure, and if an intervention is required and more than 8 h has elapsed since the last dose of LMWH, UFH can be used for PCI according to usual practice patterns. Because the anticoagulant effect of UFH can be more readily reversed than that of LMWH, UFH is preferred in patients likely to undergo CABG within 24 h.

3.2.5.3. LMWH VERSUS UFH

Nine randomized trials have directly compared LMWH with UFH (Table 17). Two trials evaluated dalteparin, another evaluated nadroparin, and 6 evaluated enoxaparin. Heterogeneity of trial results has been observed. Trials with dalteparin and nadroparin reported similar rates of death or nonfatal MI compared with UFH, whereas 5 of 6 trials of enoxaparin found point estimates for death or nonfatal MI that favored enoxaparin over UFH; the pooled OR was 0.91 (95% CI 0.83 to 0.99). The benefit of enoxaparin appeared to be driven largely by a reduction in nonfatal MI, especially in the cohort of patients who had not received any open-label anticoagulant therapy before randomization.

There are few data to assess whether the heterogeneous results are explained by different populations, study designs, various heparin dose regimens, properties of the various LMWHs (more specifically, different molecular weights and anti–factor Xa/anti–factor IIa ratios), concomitant therapies, or other unrecognized influences. Although it is tempting to compare the relative treatment effects of the different LMWH compounds, the limitations of such indirect comparisons must be recognized. The only reliable method of comparing 2 treatments is through a direct comparison in a well-designed clinical trial or series of trials. The comparison of different therapies (e.g., different LMWHs) with a common therapy (e.g., UFH) in different trials does not allow a conclusion to be made about the relative effectiveness of the different LMWHs because of the variability in both control group and experimental group event rates due to protocol differences, differences in concomitant therapies due to geographic and time variability, and the play of chance. Similar considerations apply to comparisons among platelet GP IIb/IIIa inhibitors.

In the Enoxaparin Versus Tinzaparin (EVET) trial, 2 LMWHs, enoxaparin and tinzaparin, administered for 7 d, were compared in 436 patients with UA/NSTEMI. Enoxaparin was associated with a lower rate of death/MI/recurrent angina at 7 and 30 d compared with tinzaparin (467,468). Bleeding rates were similar with the 2 LMWHs.

The advantages of LMWH preparations are the ease of subcutaneous administration and the absence of a need for monitoring. Furthermore, the LMWHs stimulate platelets less than UFH (469) and are less frequently associated with heparin-induced thrombocytopenia (456). In the ESSENCE trial, minor bleeding occurred in 11.9% of enoxaparin patients and 7.2% of UFH patients (p less than 0.001), and major bleeding occurred in 6.5% and 7.0%, respectively (169). In TIMI 11B, the rates of minor bleeding in hospital were 9.1% and 2.5%, respectively (p less than 0.001), and the rates of major bleeding were 1.5% and 1.0% ($p = 0.14$) (180). In the FRISC study, major bleeding occurred in 0.8% of patients given dalteparin and in 0.5% of patients given placebo, and minor bleeding occurred in 61 (8.2%) of 746 patients and 2 (0.3%) of 760 patients, respectively (371).

The anticoagulant effect of LMWH is less effectively reversed with protamine than that of UFH. In addition, LMWH administered during PCI does not permit monitoring of the ACT to titrate the level of anticoagulation. In the ESSENCE and TIMI 11B trials, special rules were set to discontinue enoxaparin before PCI and CABG. Because of limited experience with enoxaparin at the time the ESSENCE and TIMI 11B trials were conducted, UFH was administered during PCI to achieve ACT values of greater than 350 s. In the Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) trial, enoxaparin was compared to UFH during PCI in patients with high-risk UA/NSTEMI (423) (Fig. 12). More bleeding was observed with enoxaparin, with a statistically significant increase in TIMI-defined major bleeding (9.1% vs. 7.6%, $p = 0.008$) but a nonsignificant excess in GUSTO-defined severe bleeding (2.7% vs. 2.2%, $p = 0.08$) and transfusions (17.0% vs. 16.0%, $p = 0.16$). A post hoc analysis from SYNERGY suggested that some of the excess bleeding seen with enoxaparin could be explained by crossover to UFH at the time of PCI (470). This remains to be validated prospectively, but at the present time, it appears reasonable to minimize the risk of excessive anticoagulation during PCI by avoiding crossover of anticoagulants (i.e., maintain consistent anticoagulant therapy from the pre-PCI phase throughout the procedure itself).

An economic analysis of the ESSENCE trial suggested cost savings with enoxaparin (471). For patients who are receiving subcutaneous LMWH and in whom CABG is planned, it is recommended that LMWH be discontinued and UFH be used during the operation. Additional experience with regard to the safety and efficacy of the concom-

Table 17. Trials of LMWH Versus UFH in UA/NSTEMI

Trial (Reference)	n	LMWH/Dose	UFH	End Point/ Drug Effect	Analysis	95% CI	*p*	Major Bleeding (*p*)
FRISC (371)	1,506	(a) 6 d*: dalteparin 120 IU per kg† SC twice daily (maximum 10,000 IU) (b) During first 40 d: dalteparin 7,500 IU SC once per day	(a) 6 d: placebo (b) During first 40 d: placebo	(a) Death or new MI (6 d): LMWH 1.8%, Placebo 4.8% (b) Death or new MI (during first 40 d‡): LMWH 8%, placebo 10.7%	(a) RR 0.37 ARR 3% (b) RR 0.75 ARR 2.7%	(a) 0.20 to 0.68 (b) 0.54 to 1.03	(a) 0.001 (b) 0.07	(a) LMWH 0.8%, placebo 0.5%; ARR −0.3% (*p* = NR) (b) During first 40 d: LMWH 0.3%, placebo 0.3%; ARR 0% (*p* = NR)
ESSENCE (169)	3,171	Enoxaparin 1 mg per kg SC twice daily (minimum 48 h, maximum 8 d)	UFH IV bolus (usually 5,000 units) and continued IV infusion	(a) Death, MI, or recurrent angina at 14 d: LMWH 16.6%, UFH 19.8% (b) Death, MI, or recurrent angina at 30 d: LMWH 19.8%, UFH 23.3%	(a) OR at 14 d = 0.80 ARR 3.2% (b) OR at 30 d = 0.81 ARR 3.5%	(a) 0.67 to 0.96 (b) 0.68 to 0.96	(a) 0.019 (b) 0.016	At 30 d: LMWH 6.5%, UFH 7%; ARR 0.5% (*p* = 0.57)
FRIC (462)	1,482	(a) Days 1 to 6: dalteparin 120 IU per kg SC twice daily (b) Days 6 to 45§: dalteparin 7,500 IU SC once per day	(a) Days 1 to 6: UFH 5,000 units IV bolus and IV infusion of 1,000 units per h for 48 h (b) Days 6 to 45: placebo SC once daily	(a) Death, MI, or recurrence of angina (Days 1 to 6): LMWH 9.3%, UFH 7.6% (b) Death, MI, or recurrence of angina (Days 6 to 45): 12.3% in both the LMWH and UFH groups (a) Death or MI (Days 1 to 6): LMWH 3.9%, UFH 3.6% (b) Death or MI (Days 6 to 45): LMWH 4.3%, placebo 4.7%	(a) RR 1.18 ARR −1.7% (b) RR 1.01 ARR 0% (a) RR 1.07 ARR −0.3% (b) RR 0.92 ARR 0.4%	(a) 0.84 to 1.66 (b) 0.74 to 1.38 (a) 0.63 to 1.80 (b) 0.54 to 1.57	(a) 0.33 (b) 0.96 (a) 0.80 (b) 0.76	(a) Days 1 to 6: LMWH 1.1%, UFH 1.0%; ARR −0.1% (*p* = NR) (b) Days 6 to 45: LMWH 0.5%, placebo 0.4%; ARR −0.1% (*p* = NR)
FRAX.I.S. (463)	3,468	(a) Nadroparin 6 d: nadroparin 86 anti-Xa IU per kg IV bolus, followed by nadroparin 86 anti-Xa IU per kg SC twice daily for 6 d (b) Nadroparin 14 d: nadroparin 86 anti-Xa IU per kg IV bolus, followed by nadroparin 86 anti-Xa IU per kg SC twice daily for 14 d	(a) + (b) UFH 5,000 units IV bolus and UFH infusion at 1,250 units per h IV for 6 d (plus or minus 2 d)	Cardiac death, MI, refractory angina, recurrence of UA at Day 14: LMWH 6 d 17.8%, LMWH 14 d 20.0%, UFH 18.1%	(a) ARR 0.3% (b) ARR −1.9%	(a) −2.8 to 3.4 (b) −5.1 to 1.3	(a) 0.85 (b) 0.24	At 6 d: UFH 1.6%, LMWH 1.5%, ARR 0.1% At 14 d: UFH 1.6%, LMWH 3.5%, ARR −1.9% (*p* = 0.0035)

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Table 17. Continued

Trial (Reference)	n	LMWH/Dose	UFH	End Point/ Drug Effect	Analysis	95% CI	p	Major Bleeding (p)
TIMI 11B (180)	3,910	(a) Inpatient: enoxaparin 30 mg IV bolus immediately followed by 1 mg per kg SC every 12 h (b) Outpatient: enoxaparin 40 mg SC twice per day (patients weighing less than 65 kg) or 60 mg SC twice per day (patients weighing at least 65 kg)	(a) Inpatient: UFH 70 units per kg bolus and infusion at 15 units per h titrated to aPTT (treatment maintained for a minimum of 3 and maximum of 8 d at physician's discretion) (b) Outpatient: placebo SC twice per day	Death, MI, urgent revascularization (a) At 48 h: LMWH 5.5%, UFH 7.3% (b) 8 d: LMWH 12.4%, UFH 14.5% (c) 14 d: LMWH 14.2%, UFH 16.7% (d) 43 d: LMWH 17.3%, UFH 19.7%	(a) OR 0.75 ARR 1.8% (b) OR 0.83 ARR 2.1% (c) OR 0.82 ARR 2.5% (d) OR 0.85 ARR 2.4%	(a) 0.58 to 0.97 (b) 0.69 to 1.00 (c) 0.69 to 0.98 (d) 0.72 to 1.00	(a) 0.026 (b) 0.048 (c) 0.029 (d) 0.048	At 48 h: LMWH 0.8%, UFH 0.7%; ARR −0.1% ($p = 0.14$) End of initial hospitalization: LMWH 1.5%, UFH 1%; ARR −0.5% ($p = 0.143$) Between Day 8 and Day 43: LMWH 2.9%, placebo 2.9%; ARR 0% ($p = 0.021$)
ACUTE II‖ (464)	525	Enoxaparin 1 mg per kg SC every 12 h‖	UFH 5,000 units IV bolus and maintenance infusion at 1,000 units per h IV adjusted to aPTT	(a) Death or (b) MI at 30 d (a) LMWH 2.5%, UFH 1.9% (b) LMWH 6.7%, UFH 7.1%	(a) RR −1.3 ARR −0.6% (b) RR 0.94 ARR 0.4%	(a) 0.06 to 3.93 (b) 0.45 to 2.56	(a) 0.77 (b) 0.86	LMWH 0.3%; UFH 1%; ARR 0.7% ($p = 0.57$)
INTERACT¶ (465)	746	Enoxaparin 1 mg per kg SC every 12 h	UFH 70 units per kg IV bolus followed by continuous infusion at 15 units per kg per h	Death or MI at 30 d: LMWH 5.0%, UFH 9.0%	RR 0.55 ARR 4%	0.30 to 0.96	0.031	At 96 h: LMWH 1.8%; UFH 4.6%; ARR 2.8% ($p = 0.03$)
A to Z** (466)	3,987	Enoxaparin 1 mg per kg SC every 12 h	UFH 4,000 units IV bolus followed by 900 units per h IV infusion for patients weighing equal to or greater than 70 kg UFH 60 units per kg (maximum 4,000 units) IV bolus followed by 12 units per kg per h IV infusion for patients weighing less than 70 kg	All-cause death, MI, or refractory ischemia within 7 d of tirofiban initiation: LMWH 8.4%, UFH 9.4%	HR 0.88 ARR 1%	0.71 to 1.08	NR	LMWH 0.9%; UFH 0.4%; ARR −0.5% ($p = 0.05$)

Continued on next page

Table 17. Continued

Trial (Reference)	n	LMWH/Dose	UFH	End Point/ Drug Effect	Analysis	95% CI	p	Major Bleeding (p)
SYNERGY†† (423)	9,978	Enoxaparin 1 mg per kg SC every 12 h	UFH 60 units per kg IV bolus (maximum of 5,000 units) and followed by IV infusion of 12 units per kg per h (maximum of 1,000 units per h initially	Death or nonfatal MI during first 30 d after randomization LMWH 14.0%, UFH 14.5%,	HR 0.96 ARR 0.5%	0.86 to 1.06	0.40	TIMI minor: LMWH 12.5%, UFH 12.3%; ARR −0.2% (p = 0.80) TIMI major: LMWH 9.1%, UFH 7.6% ARR −1.5% (p = 0.008) GUSTO severe: LMWH 2.7%, UFH 2.2%; ARR −0.5% (p = 0.08)

For specific interventions and additional medications during the study, see individual study references. Major bleeding was classified as follows in the various trials: A to Z: decrease in hemoglobin of more than 5 mg per dL or intracranial or pericardial bleeding. ESSENCE: Major hemorrhage was defined as bleeding resulting in death, transfusion of at least 2 U of blood, a fall in hemoglobin of 30 g per liter or more, or a retroperitoneal, intracranial, or intraocular hemorrhage. TIMI 11B: Overt bleed resulting in death; a bleed in a retroperitoneal, intracranial, or intraocular location; a hemoglobin drop of greater than or equal to 3 g per dL; or the requirement of transfusion of at least 2 U of blood. SYNERGY: TIMI and GUSTO criteria. ACUTE II: Severity was recorded on the basis of the TIMI trial bleeding criteria. TIMI major bleeding involved a hemoglobin drop greater than 5 g per dL (with or without an identified site, not associated with coronary artery bypass grafting) or intracranial hemorrhage or cardiac tamponade. INTERACT: Major bleeding included bleeding resulting in death, or retroperitoneal hemorrhage, or bleeding at a specific site accompanied by a drop in hemoglobin greater than or equal to 3 g per dL. FRIC: A bleeding event was classified as major if it led to a fall in the hemoglobin level of at least 20 g per liter, required transfusion, was intracranial, or caused death or cessation of the study treatment. *Primary study end point was first 6 d. †Initial trial dose of 150 IU per kg SC twice daily decreased to 120 IU per kg SC twice daily due to increased bleeding during first 6 d (4 patients or 6% major bleeding episodes and 9 patients or 14% minor episodes among 63 actively treated patients). ‡Follow-up incomplete in 13 patients (8 dalteparin, 5 placebo) at their request. §Primary study outcome was Days 6 to 45. ‖All patients in ACUTE II received a tirofiban loading dose of 0.4 mcg per kg per min over 30 min, followed by a maintenance infusion at 0.1 mcg per kg per min. ¶All patients in INTERACT received eptifibatide 180 mcg per kg bolus followed by a 2.0 mcg per kg per min infusion for 48 h. **All patients enrolled in the A to Z Trial received aspirin and tirofiban. ††Patients also received glycoprotein IIb/IIIa inhibitors, aspirin, clopidogrel; patients eligible for enrollment even if LMWH or UFH given before enrollment, adjustments made to enoxaparin and UFH during percutaneous coronary intervention.

A to Z = Aggrastat to Zocor study; ACUTE II = Antithrombotic Combination Using Tirofiban and Enoxaparin; aPTT = activated partial thromboplastin time; ARR = absolute risk reduction; CI = confidence interval; ESSENCE = Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and Non-Q-Wave Myocardial Infarction; FRIC = FRagmin In unstable Coronary disease; HR = hazard ratio; INTERACT = Integrilin and Enoxaparin Randomized Assessment of Acute Coronary Syndrome Treatment; IU = international units; IV = intravenous; LD = loading dose; MD = maintenance dose; N = number of patients; LMWH = low-molecular-weight heparin; MI = myocardial infarction; NR = not reported; RR = relative risk; SC = subcutaneous; SYNERGY = Superior Yield of the New strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIA Inhibitors; TIMI 11B = Thrombolysis In Myocardial Infarction 11B; U = unit; UA = unstable angina; UFH = unfractionated heparin.

itant administration of LMWHs with GP IIb/IIIa antagonists and fibrinolytic agents is currently being acquired.

3.2.5.3.1. Extended Therapy with LMWHs. The FRISC, Fragmin in unstable coronary artery disease study (FRIC), TIMI 11B, and Fast Revascularization during InStability in Coronary artery disease-II (FRISC-II) trials evaluated the potential benefit of the prolonged administration of LMWH after hospital discharge (Table 17). In the FRISC trial, doses of dalteparin were administered between 6 d and 35 to 45 d; in FRIC, patients were rerandomized after the initial 6-d treatment period to receive dalteparin for an additional 40 d, and the outpatient treatment period lasted 5 to 6 weeks in TIMI 11B and 1 week in the FRAXiparine in Ischaemic Syndromes (FRAXIS) trial. The FRISC-II trial used a different study design. Dalteparin was administered to all patients for a minimum of 5 d (472). Patients were subsequently randomized to receive placebo or the continued administration of dalteparin twice per day for up to 90 d. Analysis of the results from the time of randomization showed a significant reduction with dalteparin in the composite end point of death or MI at 30 d (3.1% vs. 5.9%, p = 0.002) but not at 3 months (6.7% vs. 8.0%, p = 0.17). The composite of death, MI, or revascularization during the total treatment period was reduced at 3 months (29.1% vs. 33.4%, p = 0.031). The benefits of prolonged dalteparin administration were limited to patients who were managed medically and to those with elevated TnT levels at baseline. Although these results make a case for the prolonged use of an LMWH in selected patients who are managed medically or in whom angiography is delayed, their relevance to contemporary practice is less clear now that clopidogrel is used more frequently and there is a much greater tendency to proceed to an early invasive strategy.

3.2.5.4. DIRECT THROMBIN INHIBITORS

Hirudin, the prototype of the direct thrombin inhibitors, has been extensively studied but with mixed results. The GUSTO-IIb trial randomly assigned 12,142 patients with suspected MI to 72 h of therapy with either intravenous hirudin or UFH (473). Patients were stratified according to the presence of ST-segment elevation on the baseline ECG (4,131 patients) or its absence (8,011 patients). The primary end point of death, nonfatal MI, or reinfarction at 30 d occurred in 9.8% of the UFH group versus 8.9% of the hirudin group (OR 0.89, p = 0.058). For patients without ST-segment elevation, the rates were 9.1% and 8.3%, respectively (OR 0.90, p = 0.22). At 24 h, the risk of death or MI was significantly lower in the patients who received hirudin than in those who received UFH (2.1% vs. 1.3%, p = 0.001). However, the Thrombolysis and Thrombin Inhibition in Myocardial Infarction (TIMI) 9B trial of hirudin as adjunctive therapy to thrombolytic therapy in patients with STEMI showed no benefit of the drug over UFH either during study drug infusion or later (474). The GUSTO-IIb and TIMI 9B trials used hirudin doses of 0.1 mg

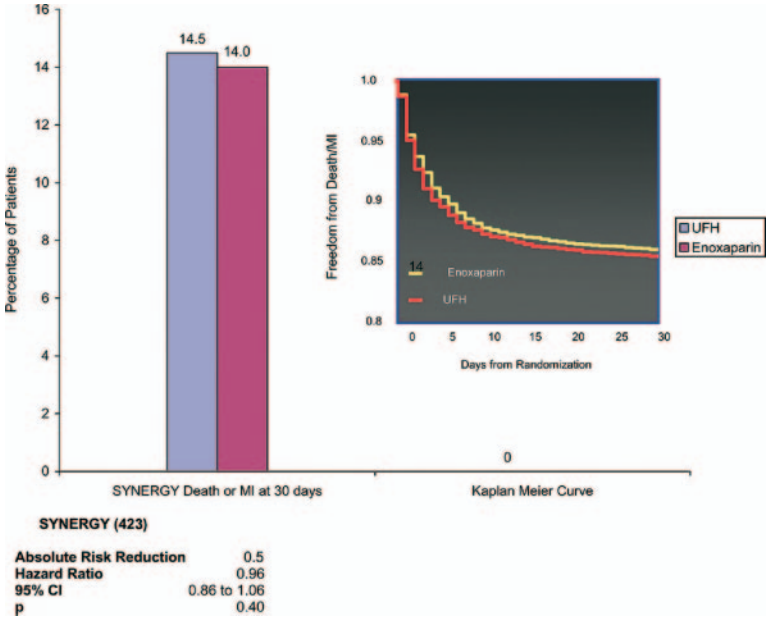

Figure 12. SYNERGY Primary Outcomes at 30 d

CI = confidence interval; MI = myocardial infarction; SYNERGY = Superior Yield of the New strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors (423); UFH = unfractionated heparin.

per kg bolus and 0.1 mg per kg per h infusion for 3 to 5 d after the documentation of excess bleeding with higher doses used in the GUSTO-IIA and TIMI 9A trials (0.6 mg per kg bolus and 0.2 mg per kg per h infusion) (473,475).

The OASIS program evaluated hirudin in patients with UA/NSTEMI. OASIS 1 (476) was a pilot trial of 909 patients that compared the low hirudin dose of 0.1 mg per kg per h infusion and the medium hirudin dose of 0.15 mg per h infusion with UFH. The latter dose provided the best results, with a reduction in the rate of death, MI, or refractory angina at 7 d (6.5% with UFH vs. 3.3% with hirudin, $p = 0.047$). This medium dose was used in the large OASIS 2 (477) trial that consisted of 10,141 patients with UA/NSTEMI who were randomized to receive UFH (5,000 IU bolus plus 15 U per kg per h) or recombinant hirudin (0.4 mg per kg bolus and 0.15 mg per kg per h) infusion for 72 h. The primary end point of cardiovascular death or new MI at 7 d occurred in 4.2% in the UFH group versus 3.6% patients in the hirudin group (RR 0.84, $p = 0.064$). A secondary end point of cardiovascular death, new MI, or refractory angina at 7 d was significantly reduced with hirudin (6.7% vs. 5.6%, RR 0.83, $p = 0.011$). There was an excess of major bleeding incidents that required transfusion with hirudin (1.2% vs. 0.7% with heparin, $p = 0.014$) but no excess in life-threatening bleeding incidents or strokes. A meta-analysis of the GUSTO-IIB, TIMI 9B, OASIS 1, and OASIS 2 trials showed a relative risk of death or MI of 0.90 ($p = 0.015$) with hirudin compared with UFH at 35 d after randomization; RR values were similar for patients receiving thrombolytic agents (0.88) and not receiving thrombolytic agents (0.90) (477).

The relative benefits of hirudin versus UFH in ACS patients undergoing PCI were evaluated in the 1,410-patient subset in GUSTO-IIb who underwent PCI during the initial drug infusion. A reduction in nonfatal MI and the composite of death and MI was observed with hirudin that was associated with a slightly higher bleeding rate (478).

Hirudin (lepirudin) is presently indicated by the US Food and Drug Administration only for anticoagulation in patients with heparin-induced thrombocytopenia (456) and for the prophylaxis of deep vein thrombosis in patients undergoing hip replacement surgery. It should be administered as a 0.4 mg per kg IV bolus over 15 to 20 s followed by a continuous intravenous infusion of 0.15 mg per kg per h, with adjustment of the infusion to a target range of 1.5 to 2.5 times the control aPTT values. Argatroban is another direct thrombin inhibitor that is approved for the management of patients with heparin-induced thrombocytopenia (479). However, in ACS, the monovalent direct thrombin inhibitors (including argatroban) are ineffective antithrombotic agents compared with UFH, and thus, argatroban should generally not be used in management of ACS (480). The recommended initial dose of argatroban is an intravenous infusion of 2 mcg per kg per min, with subsequent adjustments to be guided by the aPTT (medical management) or ACT (interventional management).

The REPLACE 2 investigators compared bivalirudin (bolus 0.75 mg per kg followed by infusion of 1.75 mg per kg per h with provisional GP IIb/IIIa inhibition) with UFH 65 U per kg bolus with planned GP IIb/IIIa inhibition in patients undergoing urgent or elective PCI (426). Only 14% had been treated for UA within 48 h before enrollment.

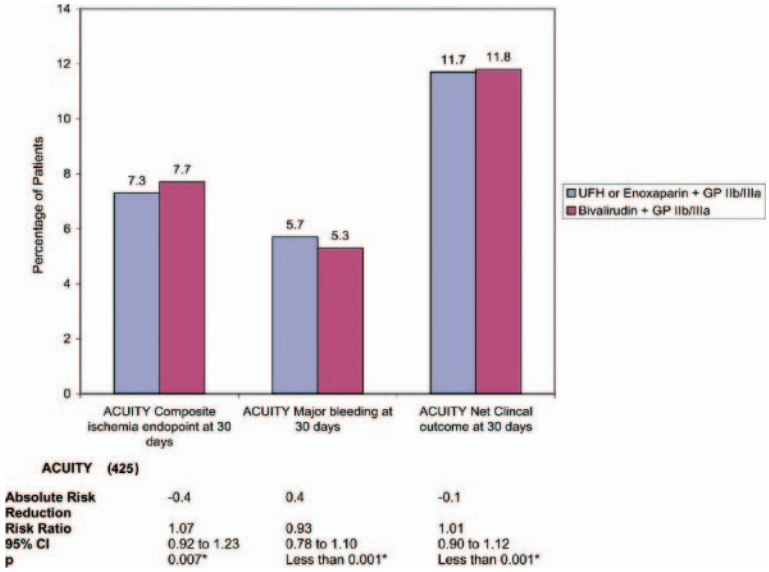

Figure 13. ACUITY Clinical Outcomes at 30 d

*p for noninferiority. ACUITY = Acute Catheterization and Urgent Intervention Triage strategY; CI = confidence interval; GP = glycoprotein; UFH = unfractionated heparin.

Prespecified definitions of noninferiority were satisfied for bivalirudin, with the benefits of a significantly lower bleeding rate (481). Follow-up through 1 year also suggested similar mortality for the 2 approaches (482).

Bivalirudin was investigated further in the ACUITY trial (425) (Figs. 13 and 14). The ACUITY trial used a 2 × 2 factorial design to compare a heparin (UFH or enoxaparin) with or without upstream GP IIb/IIIa inhibition versus bivalirudin with or without upstream GP IIb/IIIa inhibition; a third arm tested bivalirudin alone and provisional GP IIb/IIIa inhibition. The study was randomized but open-label (unblinded). The main comparisons in the ACUITY trial were of heparin with GP IIb/IIIa inhibition versus bivalirudin with GP IIb/IIIa inhibition versus bivalirudin

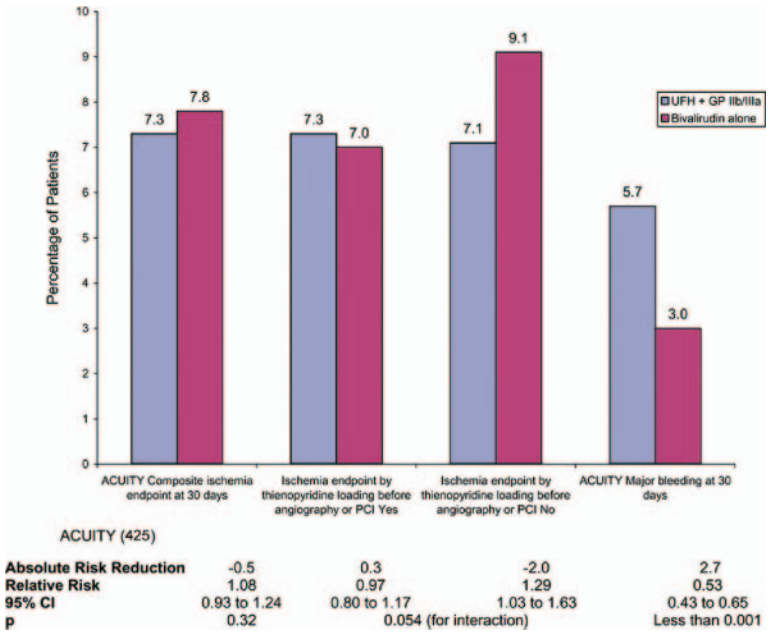

Figure 14. ACUITY Composite Ischemia and Bleeding Outcomes

ACUITY = Acute Catheterization and Urgent Intervention Triage strategY; CI = confidence interval; GP = glycoprotein; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

with provisional GP IIb/IIIa inhibition. Three primary 30-d end points were prespecified: composite ischemia, major bleeding, and net clinical outcomes (composite ischemia or major bleeding). Bivalirudin plus GP IIb/IIIa inhibitors compared with heparin plus GP IIb/IIIa inhibitors resulted in noninferior 30-d rates of composite ischemia (7.7% vs. 7.3%), major bleeding (5.3% vs. 5.7%), and net clinical outcomes (11.8% vs. 11.7%) (Fig. 13). Bivalirudin alone compared with heparin plus GP IIb/IIIa inhibitors resulted in noninferior rates of composite ischemia (7.8% vs. 7.3%, $p = 0.32$, RR 1.08, 95% CI 0.93 to 1.42), significantly reduced major bleeding (3.0% vs. 5.7%, p less than 0.001, RR 0.53, 95% CI 0.43 to 0.65), and superior 30-d net clinical outcomes (10.1% vs. 11.7% respectively, $p = 0.015$, RR 0.86, 95% CI 0.77 to 0.97). For the subgroup of 5,753 patients who did receive a thienopyridine before angiography or PCI, the composite ischemic end point occurred in 7.0% in the bivalirudin-alone group versus 7.3% in the group that received heparin plus GP IIb/IIIa inhibition (RR 0.97, 95% CI 0.80 to 1.17), whereas in the 3,304 patients who did not receive a thienopyridine before angiography or PCI, the composite ischemic event rate was 9.1% in the bivalirudin-alone group versus 7.1% in the heparin plus GP IIb/IIIa inhibition group (RR 1.29, 95% CI 1.03 to 1.63; p for interaction 0.054) (Fig. 14) (425). The Writing Committee believes that this observation introduces a note of caution about the use of bivalirudin alone, especially when there is a delay to angiography when high-risk patients who may not be represented by the ACUITY trial population are being managed, or if early ischemic discomfort occurs after the initial antithrombotic strategy has been implemented (Figs. 7, 8, and 9). The Writing Committee therefore recommends that patients meeting these criteria be treated with concomitant GP IIb/IIIa inhibitors or a thienopyridine, administered before angiography to optimize outcomes whether a bivalirudin-based or heparin-based anticoagulant strategy is used. This approach is also supported by the findings of the ACUITY timing study that showed a trend toward higher rates of ischemic events, which did not meet inferiority criteria, in the deferred GP IIb/IIIa inhibitor group compared with the upstream GP IIb/IIIa inhibitor. Death/MI/unplanned revascularization for ischemia occurred in 7.1% of routine upstream GP IIb/IIIa inhibitor group versus 7.9% of deferred selective inhibitor group; RR 1.12 (95% CI 0.97 to 1.29) (482a,482b). Similarly, in the ACUITY PCI substudy (482c,482d), subjects who did not receive a thienopyridine pre-PCI had higher rates of the composite ischemic end point in the bivalirudin-alone group compared with the heparin plus GP IIb/IIIa group. In both the REPLACE 2 and ACUITY trials, bivalirudin with provisional GP IIb/IIIa blockade was associated with a lower risk of bleeding, whereas this was not the case in ACUITY with the combination of bivalirudin and planned GP IIb/IIIa blockade, suggesting that dosing regimens and concomitant GP IIb/IIIa blockade plays an important role in bleeding risk (483). The impact of switching anticoagulants after randomization, which has been associated with excess bleeding (423,484), is unclear for bivalirudin. It should be noted that the ACUITY protocol called for angiography within 24 to 48 h of randomization and that the median time to catheterization (from the time the study drug was started) was approximately 4 h; thus, the study results of this trial cannot be extrapolated beyond the group of patients treated in an early invasive fashion.

3.2.5.5. FACTOR Xa INHIBITORS

The OASIS 5 investigators evaluated the use of fondaparinux in UA/NSTEMI (424) (Fig. 15). OASIS 5 compared 2 anticoagulant strategies given for a mean of 6 d; one of which was amended during the conduct of the trial. In OASIS 5, patients with UA/NSTEMI were randomized to a control strategy of enoxaparin 1.0 mg per kg SC twice daily (reduced to 1.0 mg per kg once daily for patients with an estimated creatinine clearance less than 30 ml per min) coupled with UFH when PCI was performed (no additional UFH if the last dose of enoxaparin was less than 6 h before). If the last dose of enoxaparin was given more than 6 h before, the recommendation was that an intravenous bolus of UFH 65 U per kg be administered if a GP IIb/IIIa inhibitor was to be used and 100 U per kg if no GP IIb/IIIa inhibitor was to be used. The opposite arm was a strategy of fondaparinux 2.5 mg SC once daily to be supplemented as follows if PCI was performed: within 6 h of the last subcutaneous dose of fondaparinux, no additional study drug was given if a GP IIb/IIIa inhibitor was used, and 2.5 mg of fondaparinux was given intravenously if no GP IIb/IIIa inhibitor was used; more than 6 h since the last dose of fondaparinux, an additional intravenous dose of fondaparinux 2.5 mg was recommended if a GP IIb/IIIa inhibitor was used or 5.0 mg IV if no GP IIb/IIIa inhibitor was used. As explained by the OASIS 5 investigators, the rationale for the recommendation to use UFH during PCI in the enoxaparin arm was based on lack of approval for enoxaparin for PCI in the US by the Food and Drug Administration, lack of available trial data on the use of enoxaparin during PCI when OASIS 5 was designed, and lack of any recommendations about the use of enoxaparin in the available ACC/AHA or ESC PCI guidelines (personal communication, OASIS 5 Investigators, July 7, 2006). The UFH dosing recommendation in the enoxaparin arm was formulated in consultation with the maker of enoxaparin and was not altered when the SYNERGY trial did not show superiority of enoxaparin over UFH (423). Of note, during the conduct of the trial, catheter-associated thrombus was reported 3 times more frequently with the fondaparinux strategy (0.9% vs. 0.3%). After approximately 12,000 of the 20,078 patients ultimately enrolled in the trial had been randomized, the protocol was amended to remind the investigators to be certain that the intravenous dose of fondaparinux was properly flushed in the line and to permit the use of open-label UFH. As described by the OASIS 5 investigators (personal communication, OASIS 5 Investi-

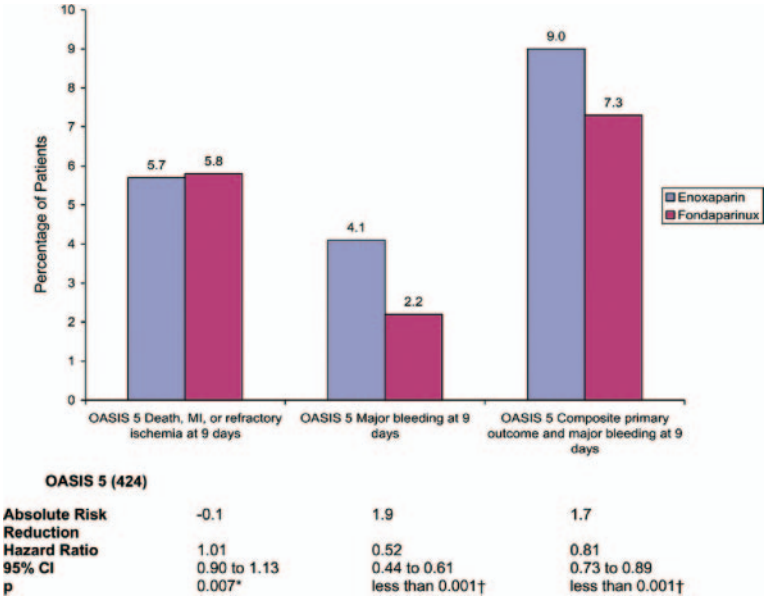

Figure 15. OASIS 5 Cumulative Risks of Death, MI, or Refractory Ischemia

*p for noninferiority. †p for superiority. CI = confidence interval; MI = myocardial infarction; OASIS 5 = Fifth Organization to Assess Strategies for Ischemic Syndromes.

gators, July 7, 2006), investigators gave open-label UFH both before and during PCI, with the dose being determined at their discretion.

The number of patients with primary outcome events at 9 d (death, MI, or refractory ischemia) was similar in the 2 groups (579 with fondaparinux [5.8%] vs. 573 with enoxaparin [5.7%]; HR in the fondaparinux group 1.01; 95% CI 0.90 to 1.13), which satisfied prespecified noninferiority criteria. The number of events that met this combined primary efficacy outcome showed a nonsignificant trend toward a lower value in the fondaparinux group at 30 d (805 vs. 864, $p = 0.13$) and at the end of the study (180 d; 1,222 vs. 1,308, $p = 0.06$; Fig. 12). The rate of major bleeding at 9 d was lower with fondaparinux than with enoxaparin (217 events [2.2%] vs. 412 events [4.1%]; HR 0.52; p less than 0.001). The composite of the primary outcome and major bleeding at 9 d favored fondaparinux (737 events [7.3%] vs. 905 events [9.0%]; HR 0.81; p less than 0.001) (Fig. 15). Fondaparinux was associated with a significantly reduced number of deaths at 30 d (295 vs. 352, $p = 0.02$) and at 180 d (574 vs. 638, $p = 0.05$). Fondaparinux also was associated with significant reductions in death, MI, and stroke ($p = 0.007$) at 180 d.

Thus, fondaparinux is another anticoagulant that has been given a Class I recommendation in the management of UA/NSTEMI, as noted in Figures 7, 8, and 9. As tested in OASIS 5, the fondaparinux (plus UFH) strategy was associated with lower bleeding rates, clearly an attractive feature given the relationship between bleeding events and increased risk of death and ischemic events (486). The excess bleeding in the enoxaparin arm may have been in part a result of the combination of enoxaparin and UFH during PCI.

At present, based on experience in both OASIS 5 and OASIS 6 (433), it appears that patients receiving fondaparinux before PCI should receive an additional anticoagulant with anti–IIa activity to support PCI (see Table 13). To date, the only anticoagulant that has been evaluated with fondaparinux during PCI is UFH, and based on limited experience, the OASIS investigators recommend an UFH dose of 50 to 60 U per kg IV when fondaparinux-treated patients are taken to PCI (personal communication, OASIS 5 Investigators, July 7, 2006). However, a cautionary note is that this UFH recommendation is not fully evidence-based, given its inconsistent and uncontrolled use in OASIS 5. Hence, additional clinical trial information is needed to establish more rigorously the safety of intravenous UFH at the time of PCI in patients receiving fondaparinux as initial medical treatment (Table 13). Because the anticoagulant effect of UFH can be more readily reversed than that of fondaparinux, UFH is preferred over fondaparinux in patients likely to undergo CABG within 24 h.

3.2.5.6. LONG-TERM ANTICOAGULATION

The long-term administration of warfarin has been evaluated in a few, mostly small studies. Williams et al. (436) randomized 102 patients with UA to UFH for 48 h followed by open-label warfarin for 6 months and reported a 65% risk reduction in the rate of MI or recurrent UA. The Antithrombotic Therapy in Acute Coronary Syndromes (ATACS) trial (369) randomized 214 patients with UA/NSTEMI to ASA alone or to the combination of ASA plus UFH followed by warfarin. At 14 d, there was a reduction in the composite end point of death, MI, and recurrent ischemia with the combination therapy (27.0% vs. 10.5%, p

= 0.004). In a small randomized pilot study of 57 patients allocated to warfarin or placebo in addition to ASA, less evidence was noted of angiographic progression in the culprit lesion after 10 weeks of treatment with warfarin (33% for placebo vs. 4% for warfarin) and more regression was observed (487). The OASIS pilot study (488) compared a fixed dosage of warfarin 3 mg per d or a moderate dose titrated to an INR of 2.0 to 2.5 in 197 patients and given for 7 months after the acute phase. Low-intensity warfarin had no benefit, whereas the moderate-intensity regimen reduced the risk of death, MI, or refractory angina by 58% and the need for rehospitalization for UA by 58%. However, these results were not reproduced in the larger OASIS 2 trial (477) of 3,712 patients randomized to the moderate-intensity regimen of warfarin or standard therapy, with all patients receiving ASA. The rate of cardiovascular death, MI, or stroke after 5 months was 7.7% with the anticoagulant and 8.4% without ($p = 0.37$) (489). Thus, the role, if any, of long-term warfarin in patients with UA/NSTEMI remains to be defined.

The Coumadin Aspirin Reinfarction Study (CARS) conducted in post-MI patients was discontinued prematurely owing to a lack of evidence of a benefit of reduced-dose ASA (80 mg per d) combined with either 1 or 3 mg of warfarin daily compared with 160 mg per d of ASA alone (490). The Combination Hemotherapy And Mortality Prevention study found no benefit to the use of warfarin (to an INR of 1.5 to 2.5) plus 81 mg per d of ASA versus 162 mg per d of ASA alone with respect to total mortality (the primary end point), cardiovascular mortality, stroke, or nonfatal MI (mean follow-up of 2.7 years) after an index MI (491). Low- or moderate-intensity anticoagulation with fixed-dose warfarin thus is not recommended for routine use after hospitalization for UA/NSTEMI. Warfarin should be prescribed, however, for UA/NSTEMI patients with established indications for warfarin, such as atrial fibrillation, left ventricular thrombus, and mechanical prosthetic heart valves.

The Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 (ASPECT-2) open-label trial randomized 999 patients after ACS to low-dose ASA, high-intensity oral anticoagulation (INR 3.0 to 4.0), or combined low-dose ASA and moderate intensity oral anticoagulation (INR 2.0 to 2.5) (492). After a median of 12 months, the primary end point of MI, stroke, or death was reached in 9% receiving ASA, 5% given anticoagulants ($p = 0.048$), and 5% receiving combination therapy ($p = 0.03$). Major and minor bleeding events occurred in 1% and 5%, 1% and 8%, and 2% and 15% of patients, respectively.

Similarly, a large (n = 3,630) Norwegian open-label study (WARIS-2) compared ASA (160 mg per d), high-intensity warfarin (INR target 2.8 to 4.2), or ASA (75 mg per d) combined with moderate-intensity warfarin (INR 2.0 to 2.5) over a mean of 4 years after MI (41% with non–Q-wave MI) (493). One third of patients underwent an intervention over the study period. The primary outcome of death, nonfatal MI, or thromboembolic stroke occurred in 20% of ASA patients, 16.7% of warfarin patients, and 15% of combination therapy patients ($p = 0.03$). The annual major bleeding rate was 0.62% in both warfarin arms and 0.17% with ASA alone (p less than 0.001). Thus, moderate-intensity warfarin with low-dose ASA appears to be more effective than ASA alone when applied to MI patients treated primarily with a noninterventional approach, but it is associated with a higher bleeding risk.

An indication for warfarin (e.g., for atrial fibrillation, mechanical prosthetic valve, or left ventricular thrombus) in addition to ASA and clopidogrel, which are indicated for most high-risk patients, arises occasionally after UA/NSTEMI. There are no prospective trials and few observational data to establish the benefit and risk of such "triple antithrombotic" therapy (494,495). In the 2004 STEMI guidelines (1), a Class IIb, Level of Evidence: C recommendation was given for the use of warfarin (INR 2.0 to 3.0) in combination with ASA (75 to 162 mg) and clopidogrel (75 mg per d) for patients with a stent implanted and concomitant indications for anticoagulation. Similarly, the 2005 PCI guidelines (2) stated that warfarin in combination with clopidogrel and low-dose ASA should be used with great caution and only when INR is carefully regulated (2.0 to 3.0). Despite a limited amount of subsequent observational data (495), the evidence base remains small, which leaves this recommendation at the Class IIb, Level of Evidence: C. When triple-combination therapy is selected for clear indications and is based on clinical judgment that benefit will outweigh the incremental risk of bleeding, then therapy should be given for the minimum time and at the minimally effective doses necessary to achieve protection. An expanded evidence base on this issue is strongly needed. Figure 11 provides recommendations for long-term management of dual- and triple-antithrombotic therapy after UA/NSTEMI.

3.2.6. Platelet GP IIb/IIIa Receptor Antagonists

The GP IIb/IIIa receptor is abundant on the platelet surface. When platelets are activated, this receptor undergoes a change in conformation that increases its affinity for binding to fibrinogen and other ligands. The binding of molecules of fibrinogen to receptors on different platelets results in platelet aggregation. This mechanism is independent of the stimulus for platelet aggregation and represents the final and obligatory pathway for platelet aggregation (496). The platelet GP IIb/IIIa receptor antagonists act by occupying the receptors, preventing fibrinogen from binding, and thereby preventing platelet aggregation. Experimental and clinical studies have suggested that occupancy of at least 80% of the receptor population and inhibition of platelet aggregation to ADP (5 to 20 micromoles per liter) by at least 80% results in potent antithrombotic effects (497). The various GP IIb/IIIa antagonists, however, possess significantly different pharmacokinetic and pharmacodynamic properties (498).

Abciximab is a Fab fragment of a humanized murine antibody that has a short plasma half-life but strong affinity for the receptor, which results in some receptor occupancy that persists in part for weeks. Platelet aggregation gradually returns to normal 24 to 48 h after discontinuation of the drug. Abciximab also inhibits the vitronectin receptor (alpha$_v$beta$_3$) on endothelial cells and the MAC-1 receptor on leukocytes (499,500). The clinical relevance of occupancy of these receptors is unknown.

Eptifibatide is a cyclic heptapeptide that contains the KGD (Lys-Gly-Asp) sequence; tirofiban is a nonpeptide mimetic of the RGD (Arg-Gly-Asp) sequence of fibrinogen (498,501–503). Receptor occupancy with these 2 synthetic antagonists is, in general, in equilibrium with plasma levels. They have half-lives of 2 to 3 h and are highly specific for the GP IIb/IIIa receptor. Platelet aggregation returns to normal in 4 to 8 h after discontinuation of these drugs, a finding that is consistent with their relatively short half-lives (504). Glycoprotein IIb/IIIa antagonists can bind to different sites on the receptor, which results in somewhat different binding properties that can modify their platelet effects and, potentially and paradoxically, activate the receptor (505). Oral antagonists to the receptor, previously under investigation, have been abandoned because of negative results of 5 large trials of 4 of these compounds (506–509).

The efficacy of GP IIb/IIIa antagonists in prevention of the complications associated with percutaneous interventions has been documented in numerous trials, many of them composed totally or largely of patients with UA (372,510–512) (Table 18). Two trials with tirofiban and 1 trial with eptifibatide have also documented their efficacy in UA/NSTEMI patients, only some of whom underwent interventions (128,130). Two trials were completed with the experimental drug lamifiban (373,513) and 1 with abciximab (514). Few direct comparative data are available for these various antiplatelet agents. The TARGET study (Do Tirofiban and ReoPro Give Similar Efficacy Trial) assessed differences in safety and efficacy of tirofiban and abciximab in 4,809 patients undergoing PCI with intended stenting (515). The composite of death, nonfatal MI, or urgent target-vessel revascularization at 30 d occurred more frequently in the tirofiban group (7.6% vs. 6.0%). The advantage of abciximab was observed exclusively among patients presenting with UA/NSTEMI (63% of the population) (515). A possible explanation for the inferior performance of in-laboratory initiation of tirofiban for PCI in the setting of ACS was an insufficient loading dose of tirofiban to achieve optimal early (periprocedural) antiplatelet effect (516).

Abciximab has been studied primarily in PCI trials, in which its administration consistently resulted in reductions in rates of MI and the need for urgent revascularization (Table 18). In subgroups of patients within those trials who had ACS, the risk of ischemic complications within the first 30 d after PCI was reduced by 60% to 80% with abciximab therapy. Two trials with abciximab specifically studied patients with acute ischemic syndromes. The CAPTURE trial enrolled patients with refractory UA (372). After angiographic identification of a culprit lesion suitable for angioplasty, patients were randomized to either abciximab or placebo administered for 20 to 24 h before angioplasty and for 1 h thereafter. The rate of death, MI, or urgent revascularization within 30 d (primary outcome) was reduced from 15.9% with placebo to 11.3% with abciximab (RR 0.71, $p = 0.012$). At 6 months, death or MI had occurred in 10.6% of the placebo-treated patients versus 9.0% of the abciximab-treated patients ($p = 0.19$). Abciximab is approved for the treatment of UA/NSTEMI as an adjunct to PCI or when PCI is planned within 24 h.

The GUSTO IV-ACS trial (514) enrolled 7,800 patients with UA/NSTEMI who were admitted to the hospital with more than 5 min of chest pain and either ST-segment depression and/or elevated TnT or TnI concentration. All received ASA and either UFH or LMWH. They were randomized to an abciximab bolus and a 24-h infusion, an abciximab bolus and a 48-h infusion, or placebo. In contrast to other trials with GP IIb/IIIa antagonists, GUSTO IV-ACS enrolled patients in whom early (less than 48 h) revascularization was not intended. At 30 d, death or MI occurred in 8.0% of patients taking placebo, 8.2% of patients taking 24-h abciximab, and 9.1% of patients taking 48-h abciximab, differences that were not statistically significant. At 48 h, death occurred in 0.3%, 0.7%, and 0.9% of patients in these groups, respectively (placebo vs. abciximab 48 h, $p = 0.008$). The lack of benefit of abciximab was observed in most subgroups, including patients with elevated concentrations of troponin who were at higher risk. Although the explanation for these results is not clear, they indicate that abciximab at the dosing regimen used in GUSTO IV-ACS is not indicated in the management of patients with UA or NSTEMI in whom an early invasive management strategy is not planned.

Tirofiban was studied in the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) (374) and Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) (130) trials. PRISM directly compared tirofiban with heparin in 3,232 patients with accelerating angina or angina at rest and ST-segment or T-wave changes and with cardiac marker elevation, a previous MI, or a positive stress test or angiographically documented coronary disease (374). The primary composite outcome (death, MI, or refractory ischemia at the end of a 48-h infusion period) was reduced from 5.6% with UFH to 3.8% with tirofiban (RR 0.67, $p = 0.01$). At 30 d, the frequency of the composite outcome was similar in the 2 groups (17.1% for UFH vs. 15.9% for tirofiban, $p = 0.34$), but a trend toward reduction in the rate of death or MI was present with tirofiban (7.1% vs. 5.8%, $p = 0.11$), and a significant reduction in mortality rates was observed (3.6% vs. 2.3%, $p = 0.02$). The benefit of tirofiban was mainly present in patients with an elevated TnI or TnT concentration at baseline.

Table 18. UA/NSTEMI Outcome of Death or Myocardial Infarction in Clinical Trials of GP IIb/IIIa Antagonists Involving More Than 1,000 Patients

			Results							
			Placebo		GP IIb/IIIa					
Trial (Year)	Study Population	Drugs	n	%	n	%	ARR, %	RR	95% CI	*p*
PCI trials										
EPIC (1994) (510)	High-risk PTCA	Abciximab	72/696	10.3	49/708	6.9*	3.4	0.68	0.47 to 0.95	0.022
EPILOG (1997) (511)	All PTCA	Abciximab	85/939	9.1	35/935	3.7*	5.4	0.41	0.28 to 0.61	Less than 0.001
CAPTURE (1997) (372)	UA	Abciximab	57/635	9.0	30/630	4.8	4.2	0.53	0.35 to 0.81	0.003
IMPACT II (1997) (517)	All PTCA	Eptifibatide	112/1328	8.4	93/1349	6.9*	1.5	0.83	0.63 to 1.06	0.134
RESTORE (1997) (518)	UA	Tirofiban	69/1070	6.4	54/1071	5.0	1.4	0.78	0.55 to 1.10	0.162
EPISTENT (1998) (512)	Elective stenting	Abciximab	83/809	10.2	38/794	4.8*	5.4	0.46	0.32 to 0.68	Less than 0.001
ESPRIT (2000) (519)	Elective stenting	Eptifibatide	104/1024	10.2	66/1040	6.3	3.9	0.62	0.46 to 0.84	0.0016
ISAR-REACT (2004) (520)	Elective stenting with clopidogrel pretreatment	Abciximab	42/1080	3.9	43/1079	4.0	−0.1	1.02	0.68 to 1.55	0.91
ACS trials										
PRISM-PLUS (1998) (130)	UA/NQWMI	Tirofiban	95/797	11.9	67/733*	9.1*	2.8	0.70	0.51 to 0.96	0.03
PRISM (1998) (374)	UA/NQWMI	Tirofiban	115/1616	7.1	94/1616	5.8†	1.3	0.82	0.61 to 1.05	0.11
PURSUIT (1998) (128)	UA/NQWMI	Eptifibatide	744/4739	15.7	670/4722	14.2*	1.5	0.90	0.82 to 1.00	0.04
PARAGON A (1998) (373)	UA/NQWMI	Lamifiban	89/758	11.7	80/755	10.6*†	1.1	0.90	0.68 to 1.20	0.48
GUSTO IV ACS (2001) (514)	UA/NQWMI	Abciximab	209/2598	8.0	450/5202‡	8.7	−0.7	1.08	0.92 to 1.26	0.36
PARAGON B (2002) (521)	UA/NQWMI	Lamifiban	296/2597	11.4	278/2628	10.6	0.8	0.94	0.77 to 1.09	0.32
ISAR-REACT (2006) (244)	UA/NSTEMI§	Abciximab	116/1010	11.5	87/1012	8.6	2.9	0.75	0.57 to 0.97	0.03
All PCI trials			624/7581	8.2	408/7606	5.4	2.8	0.65	0.58 to 0.74	Less than 0.0001
All ACS trials			1664/14 115	11.7	1726/16 668	10.4	1.3	0.86	0.81 to 0.93	Less than 0.0001
All PCI and ACS trials			2288/21 696	10.5	2134/24 274	8.8	1.7	0.83	0.83 to 0.84	Less than 0.0001

*Best treatment group selected for analysis. †Platelet GP IIb/IIIa antagonist without heparin. ‡Pooled results for 24- and 48-h infusion arms. §Used an invasive (PCI) strategy; all patients received clopidogrel.

ACS = acute coronary syndrome; CAPTURE = c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina; CI = confidence interval; EPIC = Evaluation of c7E3 for the Prevention of Ischemic Complications; EPILOG = Evaluation of PTCA and Improve Long-term Outcome by c7E3 GP IIb/IIIa receptor blockade; EPISTENT = Evaluation of Platelet IIb/IIIa Inhibitor for STENTing; ESPRIT = Enhanced Suppression of Platelet Receptor GP IIb/IIIa using Integrilin Therapy; GUSTO IV ACS = Global Use of Strategies to Open Occluded Coronary Arteries IV; IMPACT II = Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis II; ISAR-REACT = Intracoronary Stenting and Antithrombotic Regimen-Rapid Early Action for Coronary Treatment; NQWMI = non–Q-wave myocardial infarction; PARAGON = Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organization Network; PCI = percutaneous coronary intervention; PRISM = Platelet Receptor Inhibition in Ischemic Syndrome Management; PRISM-PLUS = Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms; PTCA = percutaneous transluminal coronary angioplasty; PURSUIT = Platelet Glycoprotein IIb/IIIa in Unstable 16 Angina: Receptor Suppression Using Integrilin Therapy; RESTORE = Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis; RR = risk ratio; UA = unstable angina; UA/NSTEMI = unstable angina/non–ST-elevation myocardial infarction.

The PRISM-PLUS trial enrolled 1,915 patients with clinical features of UA/NSTEMI within the previous 12 h and the presence of ischemic ST-T changes or CK and CK-MB elevation (130). Patients were randomized to tirofiban alone, UFH alone, or the combination for a period varying from 48 to 108 h. The tirofiban-alone arm was dropped during the trial because of an excess mortality rate. The combination of tirofiban and UFH compared with UFH alone reduced the primary composite end point of death, MI, or refractory ischemia at 7 d from 17.9% to 12.9% (RR 0.68, $p = 0.004$). This composite outcome also was significantly reduced at 30 d (22%, $p = 0.03$) and at 6 months (19%, $p = 0.02$). The end point of death or nonfatal MI was reduced at 7 d (43%, $p = 0.006$), at 30 d (30%, $p = 0.03$), and at 6 months (22%, $p = 0.06$). A high rate of angiography in this trial could have contributed to the important reduction in event rates. Computer-assisted analysis of coronary angiograms obtained after 48 h of treatment in PRISM-PLUS also showed a reduction in the thrombus load at the site of the culprit lesion and improved coronary flow in patients who received the combination of tirofiban and UFH (134). Tirofiban, in combination with heparin, has been approved for the treatment of patients with ACS, including patients who are managed medically and those undergoing PCI.

Eptifibatide was studied in the PURSUIT trial, which enrolled 10,948 patients who had chest pain at rest within the previous 24 h and ST-T changes or CK-MB elevation (128). The study drug was added to standard management until hospital discharge or for 72 h, although patients with normal coronary arteries or other mitigating circumstances had shorter infusions. The infusion could be continued for an additional 24 h if an intervention was performed near the end of the 72-h infusion period. The primary outcome rate of death or nonfatal MI at 30 d was reduced from 15.7% to 14.2% with eptifibatide (RR 0.91, $p = 0.042$). Within the first 96 h, a substantial treatment effect was seen (9.1% vs. 7.6%, $p = 0.01$). The benefits were maintained at 6-month follow-up. Eptifibatide has been approved for the treatment of patients with ACS (UA/NSTEMI) who are treated medically or with PCI. It is usually administered with ASA and heparin.

The cumulative event rates observed during the phase of medical management and at the time of PCI in the CAPTURE, PRISM-PLUS, and PURSUIT trials are shown in Figure 16 (523). By protocol design, almost all patients underwent PCI in CAPTURE. In PRISM-PLUS, angiography was recommended. A percutaneous revascularization was performed in 31% of patients in PRISM-PLUS and in 13% of patients in PURSUIT. Each trial showed a statistically significant reduction in the rate of death or MI during the phase of medical management; the reduction in event rates was magnified at the time of the intervention.

Although it is tempting to evaluate the drug effect by comparing patients who had intervention with those who did not, such an analysis is inappropriate. Patients who do not undergo intervention include many low-risk patients, patients who died before having the opportunity for intervention, patients with contraindications, and patients with uncomplicated courses in countries and practices that use the ischemia-guided approach; there is no way to adjust for these imbalances. Accordingly, the analysis in Figure 16 includes the event rates for all patients during the time when they were treated medically. It then begins the analysis anew in patients who underwent PCI at the time of angiography while taking drug or placebo. In the PRISM-PLUS trial, 1,069 patients did not undergo early PCI. Although tirofiban treatment was associated with a lower incidence of death, MI or death, or MI or refractory ischemia at 30 d, these reductions were not statistically significant (130). In a high-risk subgroup of these patients not undergoing PCI (TIMI risk score greater than or equal to 4) (159), tirofiban appeared to be beneficial whether patients underwent PCI (OR 0.60, 95% CI 0.35 to 1.01) or not (OR 0.69, 95% CI 0.49 to 0.99); however, no benefit was observed in patients at lower risk (181,525). In the PURSUIT trial, the impact of eptifibatide on the incidence of death or MI in the subgroup of patients who did not undergo revascularization within the first 72 h was modest and consistent with the overall trial result, although not individually significant (15.6% vs. 14.5%, $p = 0.23$) (128).

Boersma et al. performed a meta-analysis of GP IIb/IIIa antagonists of all 6 large, randomized, placebo-controlled trials (including GUSTO IV; [514]) involving 31,402 patients with UA/NSTEMI not routinely scheduled to undergo coronary revascularization (526). In the overall population, the risk of death or MI by 30 d was modestly reduced in the active treatment arms (11.8% vs. 10.8%, OR 0.91, 95% CI 0.84 to 0.98, $p = 0.015$). Treatment effect appeared to be greater among higher-risk patients with troponin elevations or ECG ST-segment depressions. Unexpectedly, no benefit was observed in women, but there was no evidence of a sex difference in treatment effect once patients were stratified by troponin concentrations (a risk reduction was seen in both men and women with elevated cTn levels). These and other data have elevated troponin level to a major factor in decision making for the use of these agents in UA/NSTEMI. Major bleeding complications were increased in the GP IIb/IIIa antagonist-treated group compared with those who received placebo (2.4% vs. 1.4%, p less than 0.0001). For special considerations about the use of GP IIb/IIIa antagonists in women, see Section 6.1.2.1.

A relationship was observed between revascularization procedures and the apparent treatment effect of GP IIb/IIIa blockade in the meta-analysis by Boersma et al. (526). Revascularization strategies were not specified by trial protocols or randomized, but 5,847 (19%) of the 31,402 patients underwent PCI or CABG within 5 d, and 11,965 patients (38%) did so within 30 d. Significant reductions in the risk of death or MI with GP IIb/IIIa blockade were observed in these subgroups (OR 0.79, 95% CI 0.68 to 0.91 for patients revascularized within 5 d; OR = 0.89, 95% CI 0.80 to 0.98 for patients revascularized within 30 d),

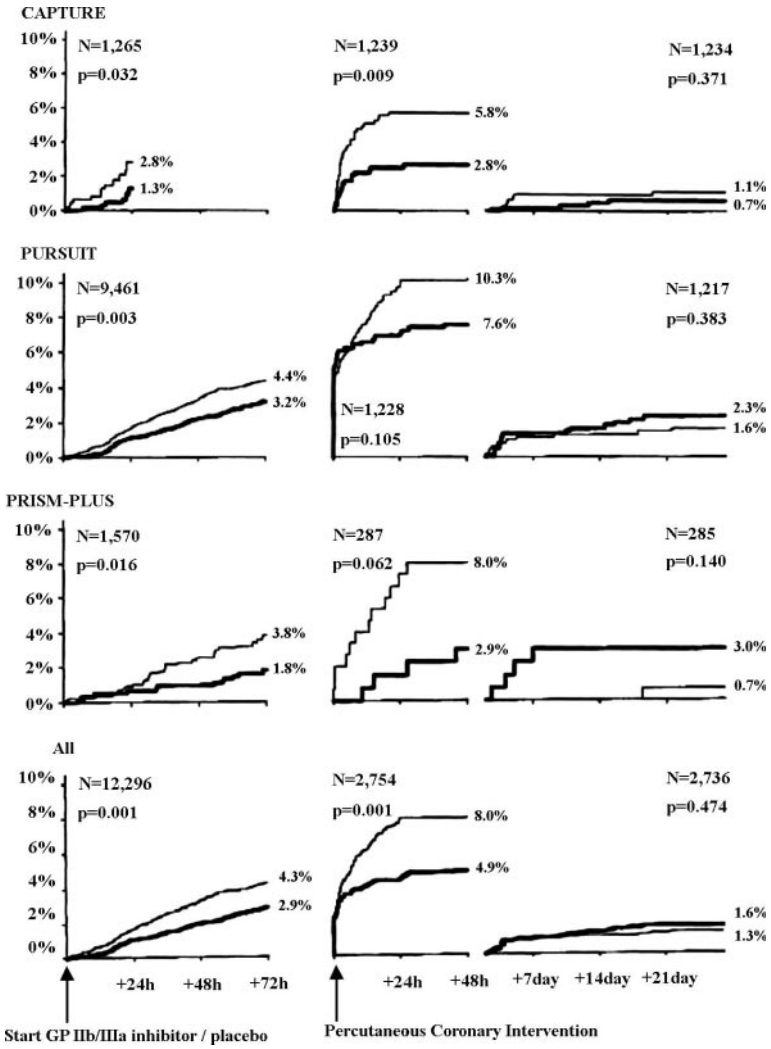

Figure 16. Kaplan-Meier Curves Showing Cumulative Incidence of Death or MI

Incidence is shown in patients randomly assigned to platelet GP IIb/IIIa receptor antagonist (bold line) or placebo. Data are derived from the CAPTURE, PURSUIT, and PRISM-PLUS trials. Left: events during the initial period of medical treatment until the moment of PCI or CABG. In the CAPTURE trial, abciximab was administered for 18 to 24 h before the PCI was performed in almost all patients as per study design; abciximab was discontinued 1 h after the intervention. In PURSUIT, a PCI was performed in 11.2% of patients during a period of medical therapy with eptifibatide that lasted 72 h and for 24 h after the intervention. In PRISM-PLUS, an intervention was performed in 30.2% of patients after a 48-h period of medical therapy with tirofiban, and the drug infusion was maintained for 12 to 24 h after an intervention. Right: events occurring at the time of PCI and the next 48 h, with the event rates reset to 0% before the intervention. Creatine kinase or creatine kinase-MB elevations exceeding 2 times the upper limit of normal were considered as infarction during medical management and exceeding 3 times the upper limit of normal for PCI-related events. Adapted from Boersma E, Akkerhuis KM, Théroux P, et al. Platelet glycoprotein IIb/IIIa receptor inhibition in non–ST-elevation acute coronary syndromes. Circulation 1999;100:2045–8 (523), CAPTURE (240), PURSUIT (172), and PRISM-PLUS (134). © Lippincott, Williams & Wilkins. CABG = coronary artery bypass graft; CAPTURE = c7E3 Fab AntiPlatelet Therapy in Unstable REfractory angina; GP = glycoprotein; MI = myocardial infarction; N = number of patients; OR = odds ratio; PCI = percutaneous coronary intervention; PRISM-PLUS = Platelet Receptor Inhibition in ischemic Syndrome Management in Patients Limited by Unstable Signs and symptoms; PURSUIT = Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy.

whereas no significant treatment effect was present in the other 19,416 patients who did not undergo coronary revascularization within 30 d (OR for death or MI 0.95, 95% CI 0.86 to 1.05). The authors concluded that the benefit of GP IIb/IIIa blockade in patients with UA/NSTEMI was "clinically most meaningful in patients at high risk of thrombotic complications" (526). The findings of this meta-analysis in the context of other trials of GP IIb/IIIa blockade during PCI suggest that GP IIb/IIIa inhibitors are of substantial benefit in patients with UA/NSTEMI who undergo PCI, are of modest benefit in patients who are not routinely scheduled to undergo revascularization (but who may do so), and are of questionable benefit in patients who do not undergo revascularization.

Although there is a temptation to use the comparison of each of these GP IIb/IIIa inhibitors with placebo to draw conclusions about relative efficacy, such an exercise could be misleading. Each trial had different entry criteria, different approaches to angiographic evaluation, and different criteria for end-point measurement and took place in different

locations in different time periods. The effects of these differences cannot be accounted for in an indirect comparison. Head-to-head (direct) comparisons are required to draw reliable conclusions about the relative efficacy of these different molecules. As noted earlier, 1 trial (TARGET) demonstrated an advantage to in-laboratory initiation of abciximab over tirofiban for UA/NSTEMI patients undergoing PCI with stenting (515). An explanation offered for this difference was an insufficient loading dose of tirofiban to achieve optimal periprocedural antiplatelet effect (516).

Treatment with a GP IIb/IIIa antagonist increases the risk of bleeding, which is typically mucocutaneous or involves the access site of vascular intervention. Unfortunately, each trial also used a different definition of bleeding and reported bleeding related to CABG differently. In the PRISM trial, with no interventions (including CABG) on treatment, major bleeding (excluding CABG) occurred in 0.4% of patients who received tirofiban and 0.4% of patients who received UFH (374). In the PRISM-PLUS trial, major bleeding according to the TIMI criteria was reported in 1.4% of patients who received tirofiban and 0.8% of patients who received placebo ($p = 0.23$), whereas PURSUIT reported major bleeding in 10.6% of patients who received eptifibatide and 9.1% of patients who received placebo ($p = 0.02$) (134,172). In the PURSUIT trial, with the exclusion of patients who underwent CABG, the rates were 3.0% with eptifibatide and 1.3% with placebo (p less than 0.001). No trials have shown an excess of intracranial bleeding with a GP IIb/IIIa inhibitor. As with the efficacy data, the temptation to make indirect comparisons should be tempered by the variability in protocol, circumstances, and definitions of the trial.

Aspirin has been used with the intravenous GP IIb/IIIa receptor blockers in all trials. A strong case also can be made for the concomitant use of heparin with GP IIb/IIIa receptor blockers. The tirofiban arm without UFH in the PRISM-PLUS trial was discontinued early because of an excess of deaths. In addition, the PURSUIT trial reported a higher event rate in the 11% of patients who were not treated with concomitant heparin (128). In a randomized comparison, a lower-dose regimen of the GP IIb/IIIa inhibitor lamifiban gave a more favorable outcome trend when combined with heparin than when administered without heparin (373). Current recommendations call for the concomitant use of heparin with GP IIb/IIIa inhibitors. Glycoprotein IIb/IIIa inhibitors can increase the ACT when combined with heparin, which means that lower doses of heparin are required to achieve a target level of anticoagulation. Moreover, trial data indicate that lower heparin doses diminish the bleeding risk associated with GP IIb/IIIa blockade in the setting of PCI, findings that likely can be extrapolated to the medical phase of management in patients with UA/NSTEMI.

Blood hemoglobin and platelet counts should be monitored and patient surveillance for bleeding should be performed daily during the administration of GP IIb/IIIa receptor blockers. Thrombocytopenia is an unusual complication of this class of agents. Severe thrombocytopenia, defined by nadir platelet counts of less than 50,000 per ml, is observed in 0.5% of patients, and profound thrombocytopenia, defined by nadir platelet counts of less than 20,000 per ml, is observed in 0.2% of patients. Although reversible, thrombocytopenia is associated with an increased risk of bleeding (527,528).

Several trials have demonstrated that GP IIb/IIIa inhibitors can be used with LMWH among patients with unstable ischemic syndromes. In the Antithrombotic Combination Using Tirofiban and Enoxaparin (ACUTE II) study (529), UFH and enoxaparin were compared in patients with UA/NSTEMI receiving tirofiban. The incidence of major and minor bleeding was similar, and there was a trend to fewer adverse events in patients receiving enoxaparin. More recently, 2 large-scale, randomized trials have examined the relative efficacy of enoxaparin versus UFH among patients with ACS. One of these, the A to Z Trial (Aggrastat to Zocor), randomized 3,987 patients who were treated with concomitant ASA and tirofiban (466). Coronary angiography was performed in 60% of patients. Nonsignificant trends toward fewer ischemic end points but more frequent bleeding events were observed with enoxaparin than with UFH therapy (466). In the larger SYNERGY trial, 10,027 patients with high-risk ACS were randomized to receive either UFH or enoxaparin (423) (Fig. 12). Glycoprotein IIb/IIIa antagonists were administered to 57% of patients, and 92% underwent coronary angiography. No advantage of enoxaparin over heparin was observed for the primary end point of death or myocardial infarction by 30 d (14.0% vs. 14.5%), but the 2 randomized therapies offered similar protection against ischemic events during PCI. Enoxaparin was associated, however, with an excess risk of TIMI major bleeding (9.1% vs. 7.6%, $p = 0.008$) (423).

The ACUITY trial investigated the combination of a GP IIb/IIIa inhibitor with bivalirudin, a direct thrombin inhibitor (see Section 3.2.2.4 and Fig. 13) (425). Glycoprotein IIb/IIIa inhibition with bivalirudin resulted in similar (noninferior) clinical outcomes compared with GP IIb/IIIa inhibition with UFH or enoxaparin.

A challenge for the current guidelines is integrating the GP IIb/IIIa studies from the 1990s with more recent studies using preangiography clopidogrel loading, newer anticoagulants, and varying degrees of patient acuity and risk/benefit. The current evidence base and expert opinion suggest that for UA/NSTEMI patients in whom an initial invasive strategy is selected, either an intravenous GP IIb/IIIa inhibitor or clopidogrel should be added to ASA and anticoagulant therapy before diagnostic angiography (upstream) for lower-risk, troponin-negative patients and that both should be given before angiography for high-risk, troponin-positive patients (Class I recommendations). For UA/NSTEMI patients in whom an initial conservative (i.e., noninvasive) strategy is selected, the evidence for benefit is less; for this strategy, the addition of eptifibatide or tirofiban to anticoagulant and oral antiplatelet therapy may be reasonable for high-risk UA/NSTEMI patients (Class IIb recommendation).

3.2.7. Fibrinolysis

The failure of intravenous fibrinolytic therapy to improve clinical outcomes in the absence of MI with ST-segment elevation or bundle-branch block was clearly demonstrated in the TIMI 11B, ISIS-2, and GISSI 1 trials (129,530,531). A meta-analysis of fibrinolytic therapy in UA/NSTEMI patients showed no benefit of fibrinolysis versus standard therapy (531a). Fibrinolytic agents had no significant beneficial effect and actually increased the risk of MI (531a). Consequently, such therapy is not recommended for the management of patients with an ACS without ST-segment elevation, a posterior-wall MI, or a presumably new left bundle-branch block (see ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction [1]).

3.3. Initial Conservative Versus Initial Invasive Strategies

RECOMMENDATIONS

CLASS I

1. An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is indicated in UA/NSTEMI patients who have refractory angina or hemodynamic or electrical instability (without serious comorbidities or contraindications to such procedures). *(Level of Evidence: B)*
2. An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is indicated in initially stabilized UA/NSTEMI patients (without serious comorbidities or contraindications to such procedures) who have an elevated risk for clinical events (see Table 11 and Sections 2.2.6 and 3.4.3). *(Level of Evidence: A)*

CLASS IIb

1. In initially stabilized patients, an initially conservative (i.e., a selectively invasive) strategy may be considered as a treatment strategy for UA/NSTEMI patients (without serious comorbidities or contraindications to such procedures) who have an elevated risk for clinical events (see Table 11 and Sections 2.2.6 and 3.4.3) including those who are troponin positive. *(Level of Evidence: B)* The decision to implement an initial conservative (vs. initial invasive) strategy in these patients may be made by considering physician and patient preference. *(Level of Evidence: C)*
2. An invasive strategy may be reasonable in patients with chronic renal insufficiency. *(Level of Evidence: C)*

CLASS III

1. An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is not recommended in patients with extensive comorbidities (e.g., liver or pulmonary failure, cancer), in whom the risks of revascularization and comorbid conditions are likely to outweigh the benefits of revascularization. *(Level of Evidence: C)*
2. An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) is not recommended in patients with acute chest pain and a low likelihood of ACS. *(Level of Evidence: C)*
3. An early invasive strategy (i.e., diagnostic angiography with intent to perform revascularization) should not be performed in patients who will not consent to revascularization regardless of the findings. *(Level of Evidence: C)*

3.3.1. General Principles

In addition to aggressive medical therapy, 2 treatment pathways have emerged for treating ACS patients. The "initial" or "early" invasive strategy, now known simply as the "invasive" strategy, triages patients to undergo an invasive diagnostic evaluation without first getting a noninvasive stress test or without failing medical treatment (i.e., an initial conservative diagnostic strategy, or sometimes now known as the "selective invasive strategy"; see below and de Winter et al. [532]). Patients treated with an invasive strategy generally will undergo coronary angiography within 4 to 24 h of admission; however, these patients also are treated with the usual UA/NSTEMI medications, including appropriate anti-ischemic, antiplatelet, and anticoagulant therapy, as outlined in Sections 3.1 and 3.2. These drugs generally are not withheld until after angiography. Within the invasive strategy, there is a subgroup of patients presenting to the ED who require urgent catheterization and revascularization in the absence of ST deviation because of ongoing ischemic symptoms or hemodynamic or rhythm instability. These patients are often rushed off to the catheterization laboratory within minutes to a few hours of arrival and are not considered appropriate candidates for a conservative strategy. Even here, appropriate medical therapy is considered; however, with these patients, the administration of GP IIb/IIIa inhibitors or clopidogrel may be delayed until the time of angiography, at a physician's discretion (Figs. 7, 8, and 9). On the other hand, the longer the interval between presentation and angiography in patients, the greater the incremental benefit of "upstream" antiplatelet therapy. In summary, the invasive strategy can be subdivided into: 1) those patients requiring urgent angiography/revascularization very soon after arrival at the ED, and 2) those with a UA/NSTEMI presentation who are designated either by patient/physician discretion or after risk assessment to benefit from "early" but nonurgent angiography/intervention.

In contrast, the "initial conservative strategy" (also referred to as "selective invasive management") calls for proceeding with an invasive evaluation only for those patients who fail medical therapy (refractory angina or angina at rest or with minimal activity despite vigorous medical therapy) or in whom objective evidence of ischemia (dynamic ECG changes, high-risk stress test) is identified. Estimating the risk for an adverse outcome is paramount for determining which strategy is best applied to an individual ACS patient. Several risk tools have been validated that are useful in guiding the type and intensity of therapy by identifying patients most likely to benefit from aggressive treatment.

One such valuable tool for risk determination is based on data from the TIMI 11B and ESSENCE trials (159) and is discussed in Section 2.2.6 and Table 8. The TIMI risk calculator is available at http://www.timi.org/.

Another simple risk-prediction tool has been validated by data from GRACE (168) (Fig. 4; Section 2.2.6). The GRACE calculator can estimate short and intermediate mortality and is useful when making diagnostic and treatment decisions for ACS patients. The GRACE clinical application tool can be downloaded to a handheld PDA to

be used at the bedside and is available at http://www.outcomes-umassmed.org/grace.

The PURSUIT, TIMI, and GRACE risk scores demonstrate good predictive accuracy for death and MI. They provide valuable information that can be used to identify patients likely to benefit from early, aggressive therapy, including intravenous GP platelet inhibitors and early coronary revascularization (174).

3.3.2. Rationale for the Initial Conservative Strategy

A few multicenter trials have shown similar outcomes with initial conservative and invasive therapeutic strategies (129,533,534). Some trials (534,535) have emphasized the early risk associated with revascularization procedures. The conservative strategy seeks to avoid the routine early use of invasive procedures unless patients experience refractory or recurrent ischemic symptoms or develop hemodynamic instability. When the conservative strategy is chosen, a plan for noninvasive evaluation is required to detect severe ischemia that occurs spontaneously or at a low threshold of stress and to promptly refer these patients for coronary angiography and revascularization when possible. In addition, as in STEMI (536), an early echocardiogram should be considered to identify patients with significant LV dysfunction (e.g., LVEF less than 0.40). Such a finding prompts consideration for angiography to identify left main or multivessel CAD, because patients with multivessel disease and LV dysfunction are at high risk and could accrue a survival benefit from CABG (537,538). In addition, a stress test (e.g., exercise or pharmacological stress) for the assessment of ischemia is recommended before discharge or shortly thereafter to identify patients who may also benefit from revascularization. The use of aggressive anticoagulant and antiplatelet agents has reduced the incidence of adverse outcomes in patients managed conservatively (see Section 3.3) (128,134,169,180,372,374,523,539). An advantage offered by the conservative strategy is that many patients stabilize on medical therapy and will not require coronary angiography. Consequently, the conservative strategy limits the use of in-hospital cardiac catheterization and may avoid costly and possibly unnecessary invasive procedures.

3.3.3. Rationale for the Invasive Strategy

For patients with UA/NSTEMI without recurrent ischemia in the first 24 h, the use of angiography provides an invasive approach to risk stratification. It can identify the 10% to 20% of patients with no significant coronary stenoses and the approximately 20% with 3-vessel disease with LV dysfunction or left main CAD. This latter group can derive a survival benefit from CABG (see Section 4). In addition, PCI of the culprit lesion has the potential to reduce the risk for subsequent hospitalization and the need for multiple antianginal drugs compared with the early conservative strategy (TIMI IIIB) (129). Just as the use of improved anticoagulant therapy and/or a platelet GP IIb/IIIa receptor blocker has improved the outcome in patients managed according to the conservative strategy, the availability of these agents also makes the invasive approach more attractive, particularly because the early hazard of PCI is lessened. The availability of GP IIb/IIIa receptor blockers also has led to 2 alternatives for the routine invasive approach: immediate angiography or deferred angiography.

3.3.4. Immediate Angiography

Excluding those in need of urgent intervention, 2 alternatives for the invasive approach have emerged: early ("immediate") or deferred angiography (i.e., with respect to a 12- to 48-h window). Some believe that proceeding immediately to angiography is an efficient approach for the ACS patient. Patients found not to have CAD may be discharged rapidly or shifted to a different management strategy. Patients with obvious culprit lesions amenable to PCI can have a procedure performed immediately, hastening discharge. Patients with left main CAD and those with multivessel disease and LV dysfunction can be sent expeditiously to undergo bypass surgery, thereby avoiding a risky waiting period. Support for immediate angiography comes from the Intracoronary Stenting with Antithrombotic Regimen Cooling-off Study (ISAR-COOL) (540). All ACS patients were treated with intensive medical therapy (including oral and intravenous antiplatelet therapy). They were randomized to immediate angiography (median time 2.4 h) or a prolonged "cooling off" period for a median of 86 h before undergoing catheterization. Patients randomized to immediate angiography had significantly fewer deaths or MIs at 30 d. Importantly, this difference in outcome was attributed to events that occurred before catheterization in the "cooling off" group, which supports the rationale for intensive medical therapy and very early angiography. Data supporting this approach are limited, but additional clinical trial results are expected in the future.

3.3.5. Deferred Angiography

In most reports that involve use of the invasive strategy, angiography has been deferred for 12 to 48 h while antithrombotic and anti-ischemic therapies are intensified. Several observational studies, as summarized in Smith et al (541) have found a lower rate of complications in patients undergoing PCI more than 48 h after admission, during which heparin and ASA were administered, than with early intervention; however, the value of medical stabilization before angiography has never been assessed formally or proven.

3.3.6. Comparison of Early Invasive and Initial Conservative Strategies

Prior meta-analyses have concluded that routine invasive therapy is better than an initial conservative or selectively invasive approach (542–544). Mehta et al. (543) concluded that the routine invasive strategy resulted in an 18% relative reduction in death or MI, including a significant reduction in MI alone. The routine invasive arm was associated with higher in-hospital mortality (1.8% vs. 1.1%), but this

disadvantage was more than compensated for by a significant reduction in mortality between discharge and the end of follow-up (3.8% vs. 4.9%). The invasive strategy also was associated with less angina and fewer rehospitalizations than with the conservative pathway. Patients undergoing routine invasive treatment also had improved quality of life.

In contrast to these finding, other studies, most recently ICTUS (Invasive versus Conservative Treatment in Unstable coronary Syndromes) (532), have favorably highlighted a strategy of selective invasive therapy (532). In ICTUS, 1,200 high-risk ACS patients were randomized to routine invasive versus selective invasive management and followed up for 1 year with respect to the combined incidence of death, MI, and ischemic rehospitalization. All patients were treated with optimal medical therapy that included ASA, clopidogrel, LMWH, and lipid-lowering therapy; abciximab was given to those undergoing revascularization. At the end of 1 year, there was no significant difference in the composite end point between groups. This study suggests that a selective invasive strategy could be reasonable in ACS patients. A possible explanation for the lack of benefit of the invasive approach in this trial (and other trials) (545) could be related to the relatively high rate of revascularization actually performed in patients treated in the selective invasive arm (47%), thereby reducing observed differences between treatment strategies (174), and to the lower event rate (lower-risk population) than in other studies. Results were unchanged during longer term follow-up (545a,545b). Nevertheless, ICTUS required troponin positivity for entry. Thus troponin alone might no longer be an adequate criterion for strategy selection, especially with increasingly sensitive troponin assays. The degree of troponin elevation and other high-risk clinical factors taken together should be considered in selecting a treatment strategy.

Other criticisms of ICTUS have included that it was relatively underpowered for hard end points and that it used a controversial definition for post-procedural MI (i.e., even minimal, asymptomatic CK-MB elevation) (532,545a,545b).

Additionally, 1-year follow-up may be inadequate to fully realize the long-term impact and benefit of the routine invasive strategy. In the RITA-3 trial (Third Randomized Intervention Treatment of Angina), 5-year but not 1-year event rates favored the early invasive arm (see Fig. 17 and text below) (546). In ICTUS, however, results were maintained during a 3-year follow-up (546a).

Thus, these guidelines recommend that in initially stabilized UA/NSTEMI patients, an initial conservative (selective invasive) strategy may be considered as a treatment option. The Writing Committee also believes that additional comparative trials of the selective invasive with the routine initial invasive strategies are indicated using aggressive contemporary medical therapies in both arms, including routine dual antiplatelet therapy in medically treated patients (as recommended in Section 5.2.1) as well as aggressive lipid lowering and other updated secondary prevention measures (as summarized in Section 5.2). Further study could provide a stronger evidence base for an initial conservative/selective invasive strategy in initially stabilized patients, as it has for stable angina patients (546a).

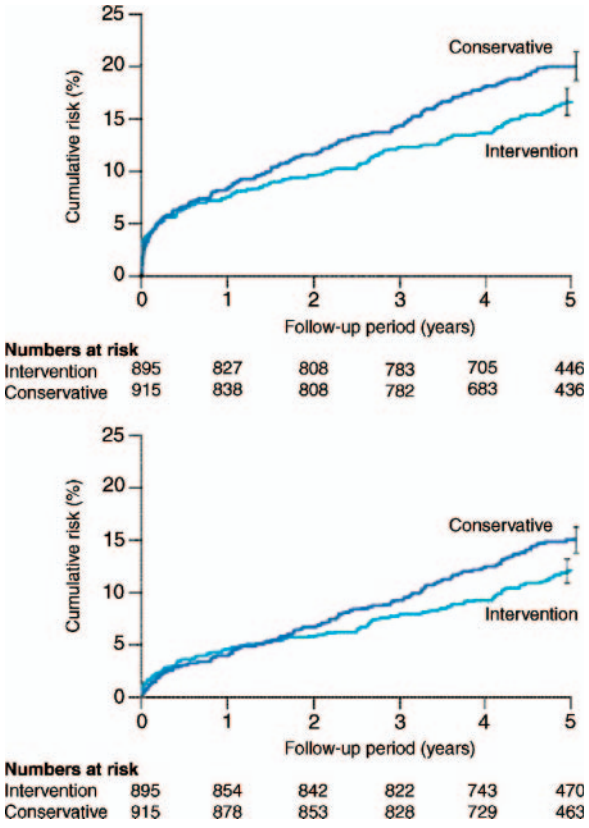

Figure 17. Cumulative Risk of Death or Myocardial Infarction or Death in RITA-3

Cumulative risk of death or myocardial infarction (top) or of death (bottom) in the RITA 3 trial of patients with non-ST acute coronary syndromes. Reprinted from The Lancet, 366, Fox KAA, Poole-Wilson P, Clayton TC, et al. 5-year outcome of an interventional strategy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial, 914–20. Copyright 2005, with permission from Elsevier (546). RITA-3 = Third Randomized Intervention Treatment of Angina trial.

Nevertheless, a meta-analysis of contemporary randomized trials in NSTEMI, including ICTUS, currently supports a long-term mortality and morbidity benefit of an early invasive as compared with an initial conservative strategy (547). Nonfatal MI at 2 years (7.6% vs. 9.1%, respectively; RR 0.83, 95% CI 0.72 to 0.96, $p = 0.012$) and hospitalization (at 13 months; RR = 0.69, 95% CI 0.65 to 0.74, p less than 0.0001) also were reduced by an early invasive strategy (Fig. 18). A separate review of contemporary randomized trials in the stent era using the Cochrane database arrived at similar conclusions (548). Details of selected contemporary trials of invasive versus conservative strategies follow.

In the FRISC-II study, 3,048 ACS patients were treated with dalteparin for 5 to 7 d (245). Of these patients, 2,457 who qualified were then randomized (2 × 2 factorial design)

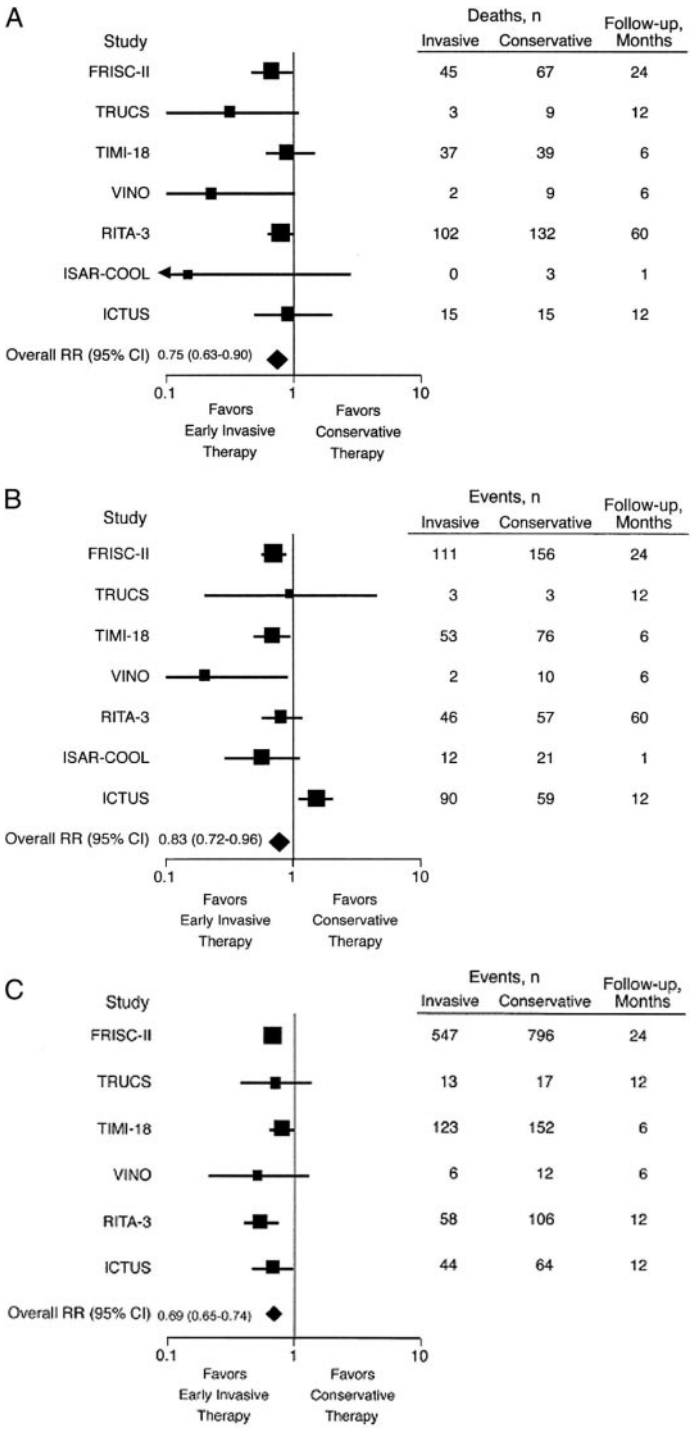

Figure 18. Relative Risk of Outcomes With Early Invasive Versus Conservative Therapy in UA/NSTEMI

A: Relative risk of all-cause mortality for early invasive therapy compared with conservative therapy at a mean follow-up of 2 years. B: Relative risk of recurrent nonfatal myocardial infarction for early invasive therapy compared with conservative therapy at a mean follow-up of 2 years. C: Relative risk of recurrent unstable angina resulting in rehospitalization for early invasive therapy compared with conservative therapy at a mean follow-up of 13 months. Modified from the Journal of the American College of Cardiology, 48, Bavry AA, Kumbhani DJ, Rassi AN, Bhatt DL, Askari AT. Benefit of early invasive therapy in acute coronary syndromes a meta-analysis of contemporary randomized clinical trials, 1319–25. Copyright 2006, with permission from Elsevier (547). CI = confidence interval; FRISC-II = FRagmin and fast Revascularization during InStability in Coronary artery disease; ICTUS = Invasive versus Conservative Treatment in Unstable coronary Syndromes; ISAR-COOL = Intracoronary Stenting with Antithrombotic Regimen COOLing-off study; RITA-3 = Third Randomized Intervention Treatment of Angina trial; RR = relative risk; TIMI-18 = Thrombolysis In Myocardial Infarction-18; TRUCS = Treatment of Refractory Unstable angina in geographically isolated areas without Cardiac Surgery; UA/NSTEMI = unstable angina/non–ST-elevation myocardial infarction; VINO = Value of first day angiography/angioplasty In evolving Non-ST segment elevation myocardial infarction: Open multicenter randomized trial.

to continue to receive dalteparin or placebo (double blind) and to receive either a noninvasive or an invasive treatment strategy, with coronary angiography and revascularization, if appropriate, performed within 7 d of admission. At 6 months, there were no differences between continued dalteparin compared with placebo. However, death or MI occurred in 9.4% of patients assigned to the invasive strategy versus 12.1% of those assigned to the noninvasive strategy (p less than 0.03). At 1 year, the mortality rate in the invasive strategy group was 2.2% compared with 3.9% in the noninvasive strategy group ($p = 0.016$) (549). It may be concluded from FRISC-II that patients with UA/NSTEMI who are not at very high risk for revascularization and who first receive an average of 6 d of treatment with LMWH, ASA, nitrates, and beta blockers have a better outcome at 6 months with a (delayed) routine invasive approach than with a routine conservative approach, with very low revascularization rates. Long-term outcomes of the FRISC-II trial have been published recently (550). At 5 years, the invasive strategy was favored for the primary end point of death or nonfatal MI (HR 0.81, $p = 0.009$). Benefit was confined to men, nonsmokers, and patients with 2 or more risk factors.

In the TACTICS-TIMI 18 trial (182), 2,220 patients with UA or NSTEMI were treated with ASA, heparin, and the GP IIb/IIIa inhibitor tirofiban. They were randomized to an early invasive strategy with routine coronary angiography within 48 h followed by revascularization if the coronary anatomy was deemed suitable or to a more conservative strategy. In the latter group, catheterization was performed only if the patient had recurrent ischemia or a positive stress test. Death, MI, or rehospitalization for ACS at 6 months occurred in 15.9% of patients assigned to the invasive strategy versus 19.4% assigned to the more conservative strategy ($p = 0.025$). Death or MI (182) was also reduced at 6 months (7.3% vs. 9.5%, p less than 0.05). The beneficial effects on outcome were observed in medium- and high-risk patients, as defined by an elevation of TnT greater than 0.01 ng per ml, the presence of ST-segment deviation, or a TIMI risk score greater than 3 (159). In the absence of these high-risk features, outcomes in patients assigned to the 2 strategies were similar, which emphasizes the critical importance of appropriate risk stratification. Rates of major bleeding were similar, and lengths of hospital stay were reduced in patients assigned to the invasive strategy. The benefits of the invasive strategy were achieved at no significant increase in the costs of care over the 6-month follow-up period.

Thus, both the FRISC-II (245) and TACTICS-TIMI 18 (182) trials showed a benefit in patients assigned to the invasive strategy. In contrast to earlier trials, a large majority of patients undergoing PCI in these 2 trials received coronary stenting as opposed to balloon angioplasty alone. Also, there was a differential rate of thienopyridine use between the 2 arms; only stented patients were treated. In FRISC-II, the invasive strategy involved treatment for an average of 6 d in the hospital with LMWH, ASA, nitrates, and beta blockers before coronary angiography, an approach that would be difficult to adopt in US hospitals. In TACTICS-TIMI 18, treatment included the GP IIb/IIIa antagonist tirofiban, which was administered for an average of 22 h before coronary angiography. The routine use of the GP IIb/IIIa inhibitor in this trial may have eliminated the excess risk of early (within 7 d) MI in the invasive arm, an excess risk that was observed in FRISC-II and other trials in which there was no routine "upstream" use of a GP IIb/IIIa blocker. Therefore, an invasive strategy is associated with a better outcome in UA/NSTEMI patients at high risk as defined in Table 11 and as demonstrated in TACTICS-TIMI 18 when a GP IIb/IIIa inhibitor is used (182). Although the benefit of intravenous GP IIb/IIIa inhibitors is established for UA/NSTEMI patients undergoing PCI, the optimal time to commence these drugs before the procedure has not been established. In the PURSUIT trial (128), in patients with UA/NSTEMI who were admitted to community hospitals, the administration of eptifibatide was associated with a reduced need for transfer to tertiary referral centers and improved outcomes (551).

The RITA-3 trial (546) compared early and conservative therapy in 1,810 moderate-risk patients with ACS. Patients with positive cardiac biomarkers (CK-MB greater than 2 times the upper limit of normal at randomization) were excluded from randomization, as were those with new Q waves, MI within 1 month, PCI within 1 year, and any prior CABG. The combined end point of death, nonfatal MI, and refractory angina was reduced from 14.5% to 9.6% by early invasive treatment. The benefit was driven primarily by a reduction in refractory angina. There was a late divergence of the curves, with reduced 5-year death and MI in the early invasive arm (Fig. 17).

In the VINO trial (Value of first day angiography/angioplasty In evolving Non-ST segment elevation myocardial infarction: Open multicenter randomized trial) (522), 131 patients with NSTEMI were randomized to cardiac catheterization on the day of admission versus conservative therapy. Despite the fact that 40% of the conservatively treated patients crossed over to revascularization by the time of the 6-month follow-up, there was a significant reduction in death or reinfarction for patients assigned to early angiography and revascularization (6% vs. 22%).

The ISAR-COOL trial (540) randomized 410 intermediate- to high-risk patients to very early angiography and revascularization versus a delayed invasive strategy. All patients were treated with intensive medical therapy that included ASA, heparin, clopidogrel (600-mg loading dose), and the intravenous GP IIb/IIIa receptor inhibitor tirofiban. In the very early arm, patients underwent cardiac catheterization at a mean time of 2.4 h versus 86 h in the delayed invasive arm. The very early invasive strategy was associated with significantly better outcome at 30 d, measured by reduction in death and large MI (5.9% vs. 11.6%). More importantly, the benefit seen was attributable to a reduction in events before cardiac catheteriza-

tion, which raises the possibility that there is a hazard associated with a "cooling-down" period.

3.3.7. Subgroups

TACTICS-TIMI 18 demonstrated a reduction in the 6-month end point of death or MI in older adult ACS patients. With respect to gender, controversy exists over revascularization treatment differences between men and women with ACS. The FRISC-II trial showed a benefit of early revascularization in men for death or MI that was not observed for women (552). In contrast, death, MI, or rehospitalization rates were reduced for both men and women in TACTICS-TIMI 18 (182). Furthermore, an observational study reported that women actually did better than men with early interventional therapy for UA/NSTEMI (553). Finally, RITA-3 (546) showed that the routine strategy of invasive evaluation resulted in a beneficial effect in men that was not seen in women. Additional research is required to further clarify these diverse observations (554).

3.3.8. Care Objectives

The objective is to provide a strategy that has the most potential to yield the best clinical outcome and improve long-term prognosis. The purpose of coronary angiography is to provide detailed information about the size and distribution of coronary vessels, the location and extent of atherosclerotic obstruction, and the suitability for revascularization. The LV angiogram, which is usually performed along with coronary angiography, provides an assessment of the extent of focal and global LV dysfunction and of the presence and severity of coexisting disorders (e.g., valvular or congenital lesions). A detailed discussion of revascularization is presented in Section 4 of these guidelines, as well as in the ACC/AHA Guidelines for Percutaneous Coronary Intervention (2) and the ACC/AHA Guideline Update for Coronary Artery Bypass Graft Surgery (555). Although general guidelines can be offered, the selection of appropriate procedures and the decision to refer patients for revascularization require both clinical judgment and counseling with the patient and the patient's family regarding expected risks and benefits.

Although not conducted in patients with UA/NSTEMI, the following studies have addressed the value of stress testing in guiding therapy. The DANish trial in Acute Myocardial Infarction (DANAMI) studied 503 patients with inducible ischemia (i.e., a positive exercise stress test) after fibrinolytic therapy for first MI and compared an ischemia-guided invasive strategy with a conservative strategy (556). The invasive strategy in the post-MI patients with inducible ischemia resulted in a reduction in the incidence of reinfarction, hospitalizations for UA, and stable angina. Similarly, in the Asymptomatic Cardiac Ischemia Pilot (ACIP) study (557,558), 558 clinically stable patients with ischemia on stress testing and during daily life (ST-segment depression on exercise treadmill testing or perfusion abnormality on radionuclide pharmacological stress test if unable to exercise, in addition to ST-segment depression on ambulatory ECG monitoring), most of whom had angina in the previous 6 weeks, were randomized to 1 of 3 initial treatment strategies: symptom-guided medical care, ischemia-guided medical care, or revascularization. More than one third of these patients had "complex" stenoses on angiography. Those randomized to early revascularization experienced less ambulatory ischemia at 12 weeks than did those randomized to initial medical care in whom revascularization was delayed and symptom driven.

After either STEMI or NSTEMI, the SWISSI II (Swiss Interventional Study of Silent Ischemia Type II) study, which randomized 201 patients with silent ischemia, demonstrated by stress imaging, to either revascularization with PCI or anti-ischemic drug therapy and followed them for an average of 10 years. Survival free of cardiac death, nonfatal MI, or symptom-driven revascularization was significantly reduced in the PCI group. Though relatively small, the study supports the use of stress testing after UA/NSTEMI for guiding the selection of invasive evaluation in UA/NSTEMI patients treated with an initial conservative strategy (558a).

In ACS patients with UA/NSTEMI, the purpose of noninvasive testing is both to identify ischemia and to identify candidates at high risk for adverse outcomes and to direct them to coronary angiography and revascularization when possible. However, neither randomized trials (129,245,533,534) nor observational data (559) uniformly support an inherent superiority for the routine use of coronary angiography and revascularization (see Section 4). Accordingly, the decision regarding which strategy to pursue for a given patient should be based on the patient's estimated outcome risk assisted by clinical and noninvasive test results, available facilities, previous outcome of revascularization by the team available in the institution in which the patient is hospitalized, and patient preference.

Coronary angiography can enhance prognostic stratification. This information can be used to guide medical therapy and to plan revascularization therapy, but it is important to emphasize that an adverse outcome in ACS is very time dependent and that after 1 to 2 months, the risk for adverse outcome is essentially the same as that for low-risk chronic stable angina (Fig. 17). Several older studies in patients with stable angina, including the Second Randomized Intervention Treatment of Angina (RITA-2) trial (535), have found a higher early risk of death or MI with an interventional strategy than with medical management alone. Thus, the timing of coronary angiography and revascularization is critically important if patients at high risk are to benefit. Unfortunately, the total number of operative complications is increased when revascularization procedures are performed routinely, because some patients who are not in need of revascularization will be exposed to its hazards. However, contemporary use of aggressive medical therapy in UA/NSTEMI, including oral and intravenous antiplatelet

agents and anticoagulant agents, has lessened the early hazard and risk for ischemic complications in patients undergoing early invasive procedures.

Patients with UA/NSTEMI often can be divided into different risk groups on the basis of their initial clinical presentation. The TIMI, PURSUIT, and GRACE scores are useful clinical tools for assigning risk to patients presenting with UA/NSTEMI (Table 8; Fig. 4; see Section 2.2.6.).

Risk stratification in turn identifies patients who are most likely to benefit from subsequent revascularization. For example, patients with left main disease or multivessel CAD with reduced LV function are at high risk for adverse outcomes and are likely to benefit from surgical bypass. Clinical evaluation and noninvasive testing will aid in the identification of most patients in the high-risk subset, because they often have 1 or more of the following high-risk features: advanced age (greater than 70 years), prior MI, revascularization, ST-segment deviation, HF or depressed resting LV function (i.e., LVEF less than or equal to 0.40) on noninvasive study, or noninvasive stress test findings. The presence of any of these risk factors or of diabetes mellitus aids in the identification of high-risk patients who could benefit from an invasive strategy.

The majority of patients presenting with UA/NSTEMI, however, do not fall into the very high-risk group and do not have findings that typically portend a high risk for adverse outcomes. Accordingly, they are not likely to receive the same degree of benefit from routine revascularization afforded to high-risk patients, and an invasive study is optional for those at lower risk and can be safely deferred pending further clinical developments. Decisions regarding coronary angiography in patients who are not high risk according to findings on clinical examination and noninvasive testing can be individualized on the basis of patient preferences and the degree to which they are affected by clinical symptoms.

The data on which recommendations for invasive or conservative strategy recommendations are based come from several randomized trials. Older trials included TIMI IIIB (129,561), Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) (534), and Medicine versus Angiography in Thrombolytic Exclusion (MATE) (533). More recent trials, relevant to contemporary practice, include FRISC-II (245), TACTICS-TIMI 18 (182), VINO (522), RITA-3 (546), ISAR-COOL (540), and ICTUS (532); a large, prospective, multinational registry, the OASIS registry (559); and several meta-analyses (542–544). See Section 3.3.1.5 for a detailed description of these trials and the more recent meta-analyses (543,547).

Some selected areas require additional comment. In a patient with UA, a history of prior PCI within the past 6 months suggests the presence of restenosis, which often can be treated effectively with repeat PCI. Coronary angiography without preceding functional testing is generally indicated. Patients with prior CABG represent another subgroup for whom a strategy of early coronary angiography is usually indicated. The complex interplay between the progression of native coronary disease and the development of graft atherosclerosis with ulceration and embolization is difficult to untangle noninvasively; these considerations argue for early coronary angiography. In addition, patients with known or suspected reduced LV systolic function, including patients with prior anterior Q-wave MIs, those with known depressed LV function, and those who present with HF, have sufficient risk that the possibility of benefit from revascularization procedures merits early coronary angiography without preceding functional testing.

In patients with UA/NSTEMI, coronary angiography typically shows the following profile: 1) no severe epicardial stenosis in 10% to 20% with a sex differential, 2) 1-vessel stenosis in 30% to 35%, 3) multivessel stenosis in 40% to 50%, and 4) significant (greater than 50%) left main stenosis in 4% to 10%. In the early invasive strategy in TIMI IIIB, no critical obstruction (less than 60% diameter stenosis) was found in 19% of patients, 1-vessel stenosis in 38%, 2-vessel stenosis in 29%, 3-vessel stenosis in 15%, and left main stenosis (greater than 50%) in 4% (564). Complex plaques are usually believed to be responsible for the culprit lesions. These usually are eccentric and sometimes have irregular borders and correlate with intracoronary thrombi and an increased risk of recurrent ischemia at rest, MI, and cardiac death (563). Similar findings were noted in more than 80% of the patients in the VANQWISH trial, and more than 1 complex lesion was found in most patients (534). Interestingly, in TIMI IIIB, many of the patients without severe stenosis had reduced contrast clearance, which suggests microvascular dysfunction (564), which can contribute to impaired myocardial perfusion.

Appropriate treatment for women presenting with ACS might be different from that in men (see also Section 6.1). In FRISC-II and RITA-3, an improved outcome in the early invasive arm was seen only in men, whereas the benefit of early revascularization was equivalent in men and women in the TACTICS-TIMI 18 (182) trial provided that the troponin level was elevated. In contrast, low-risk women tended to have worse outcomes, including a higher risk of major bleeding, with early revascularization therapy, whereas low-risk men were neither harmed nor benefited by this strategy (565). Most studies showed that women were more likely than men to have either normal vessels or noncritical stenoses. High-risk women also were more likely to have elevation of CRP and BNP and less often had elevated troponin (182,565). Women with any positive biomarker benefited from invasive therapy, whereas those without elevated CRP, BNP, or troponin did better with a conservative approach (see Section 6.1).

Patients with severe 3-vessel stenosis and reduced LV function and those with left main stenosis should be considered for early CABG (see Section 4). In low-risk patients, quality of life and patient preferences should be

given considerable weight in the selection of a treatment strategy. Low-risk patients whose symptoms do not respond well to maximal medical therapy and who experience poor quality of life and functional status and are prepared to accept the risks of revascularization should be considered for revascularization.

The discovery that a patient does not have significant obstructive CAD should prompt consideration of whether the symptoms represent another cause of cardiac ischemia (e.g., syndrome X, coronary spasm, coronary embolism, or coronary artery dissection; see Section 6) or pericarditis/myocarditis or are noncardiac in origin. There is a distinction between normal coronaries and vessels with less than 50% stenoses but with atherosclerotic plaque present, which might be demonstrated to be extensive on coronary intravascular ultrasound. The latter can include visualization of a culprit ulcerated plaque. Noncardiac syndromes should prompt a search for the true cause of symptoms. Unfortunately, many such patients continue to have recurrent symptoms, are readmitted to the hospital, can become disabled, and continue to consume health care resources even with repeated coronary angiography (566,567).

It is not presently possible to define the extent of comorbidity that would, in every case, make referral for coronary angiography and revascularization inappropriate. The high-risk patient with significant comorbidities requires thoughtful discussion among the physician, patient, and family and/or patient advocate. A decision for or against revascularization must be made on a case-by-case basis.

Examples of extensive comorbidity that usually preclude revascularization include 1) advanced or metastatic malignancy with a projected life expectancy of 1 year or less, 2) intracranial pathology that contraindicates the use of systemic anticoagulation or causes severe cognitive disturbance (e.g., Alzheimer's disease) or advanced physical limitations, 3) end-stage cirrhosis with symptomatic portal hypertension (e.g., encephalopathy, visceral bleeding), and 4) CAD that is known from previous angiography not to be amenable to revascularization. This list is not meant to be all-inclusive. More difficult decisions involve patients with significant comorbidities that are not as serious as those listed here; examples include patients who have moderate or severe renal failure but are stable with dialysis.

Consultation with an interventional cardiologist and a cardiac surgeon before coronary angiography is advised to define technical options and likely risks and benefits. The operators who perform coronary angiography and revascularization and the facility in which these procedures are performed are important considerations, because the availability of interventional cardiologists and cardiac surgeons who are experienced in high-risk and complex patients is essential. As a general principle, the potential benefits of coronary angiography and revascularization must be carefully weighed against the risks and the conflicting results of the clinical trials and registries. The Writing Committee endorses further research into techniques that could reduce bleeding (e.g., radial access and smaller sheath sizes) (568) and the proper selection and dosing of drugs to minimize bleeding in patients with UA/NSTEMI.

3.4. Risk Stratification Before Discharge

RECOMMENDATIONS

CLASS I

1. **Noninvasive stress testing is recommended in low-risk patients (Table 7) who have been free of ischemia at rest or with low-level activity and of HF for a minimum of 12 to 24 h.** ***(Level of Evidence: C)***
2. **Noninvasive stress testing is recommended in patients at intermediate risk (Table 7) who have been free of ischemia at rest or with low-level activity and of HF for a minimum of 12 to 24 h.** ***(Level of Evidence: C)***
3. **Choice of stress test is based on the resting ECG, ability to perform exercise, local expertise, and technologies available. Treadmill exercise is useful in patients able to exercise in whom the ECG is free of baseline ST-segment abnormalities, bundle-branch block, LV hypertrophy, intraventricular conduction defect, paced rhythm, preexcitation, and digoxin effect.** ***(Level of Evidence: C)***
4. **An imaging modality should be added in patients with resting ST-segment depression (greater than or equal to 0.10 mV), LV hypertrophy, bundle-branch block, intraventricular conduction defect, preexcitation, or digoxin who are able to exercise. In patients undergoing a low-level exercise test, an imaging modality can add sensitivity.** ***(Level of Evidence: B)***
5. **Pharmacological stress testing with imaging is recommended when physical limitations (e.g., arthritis, amputation, severe peripheral vascular disease, severe chronic obstructive pulmonary disease, or general debility) preclude adequate exercise stress.** ***(Level of Evidence: B)***
6. **Prompt angiography without noninvasive risk stratification should be performed for failure of stabilization with intensive medical treatment.** ***(Level of Evidence: B)***
7. **A noninvasive test (echocardiogram or radionuclide angiogram) is recommended to evaluate LV function in patients with definite ACS who are not scheduled for coronary angiography and left ventriculography.** ***(Level of Evidence: B)***

The management of ACS patients requires continuous risk stratification. Important prognostic information is derived from careful initial assessment, the patient's course during the first few days of management, and the patient's response to anti-ischemic and antithrombotic therapy. The Braunwald classification (14,260) has been validated prospectively and represents an appropriate clinical instrument to help predict outcome (569). Angina at rest, within 48 h in the absence of an extracardiac condition (primary UA; Braunwald Class III), and UA in the early postinfarction period (Braunwald class C), along with age, male sex, hypertension, and maximal intravenous antianginal/antiischemic therapy, were independent predictors for death or nonfatal MI. The baseline ECG on presentation was also found to be extremely useful for risk stratification in the

TIMI III registry (199), as discussed in Section 2.2.6.2, and in the RISC (Research on InStability in Coronary artery disease) study group (570). In a more recent database of 12,142 patients presenting within 12 h of the onset of ischemic symptoms, the ECG at presentation allowed individualized risk stratification across the spectrum of ACS (127) (Fig. 19). In many cases, noninvasive stress testing provides a very useful supplement to such clinically based risk assessment. In addition, as pointed out previously, troponins are very helpful in risk assessment. Some patients, however, are at such high risk for an adverse outcome that noninvasive risk stratification would not be likely to identify a subgroup with sufficiently low risk to avoid coronary angiography to determine whether revascularization is possible. These patients include those who, despite intensive medical therapy, manifest recurrent rest angina, hemodynamic compromise, or severe LV dysfunction. Such patients should be considered directly for early coronary angiography without noninvasive stress testing; however, referral for coronary angiography is not reasonable if they are unwilling to consider revascularization or have severe complicating illnesses that preclude revascularization. Other patients may have such a low likelihood of CAD after initial clinical evaluation that even an abnormal test finding is unlikely to prompt additional therapy that would further reduce risk (e.g., a 35-year-old woman without CAD risk factors). Such patients would ordinarily not be considered for coronary angiography and revascularization unless the diagnosis of UA/NSTEMI is unclear. The majority of patients presenting with UA/NSTEMI do not fall into these categories and are accordingly reasonable candidates for risk stratification with noninvasive testing.

Determination of patient risk on the basis of a validated scoring algorithm (e.g., from the TIMI, GRACE, or PURSUIT trial data) can be valuable for identifying high-risk patients (see Section 2.2.6 and Table 8). They also can assist in selecting those who can benefit most from more aggressive therapies, such as LMWH or an invasive treatment strategy (see Section 3.4.1).

3.4.1. Care Objectives

The goals of noninvasive testing are to 1) determine the presence or absence of ischemia in patients with a low or intermediate likelihood of CAD and 2) estimate prognosis. This information is key for the development of further diagnostic steps and therapeutic measures.

A detailed discussion of noninvasive stress testing in CAD is presented in the ACC/AHA Guidelines for Exercise Testing, ACC/AHA Guidelines for the Clinical Use of Cardiac Radionuclide Imaging, and ACC/AHA Guidelines for the Clinical Application of Echocardiography (4,571–573) (Tables 19, 20, and 21). Briefly, the provocation of ischemia at a low workload (574) or a high-risk treadmill score (i.e., greater than or equal to 11) (575) implies severe

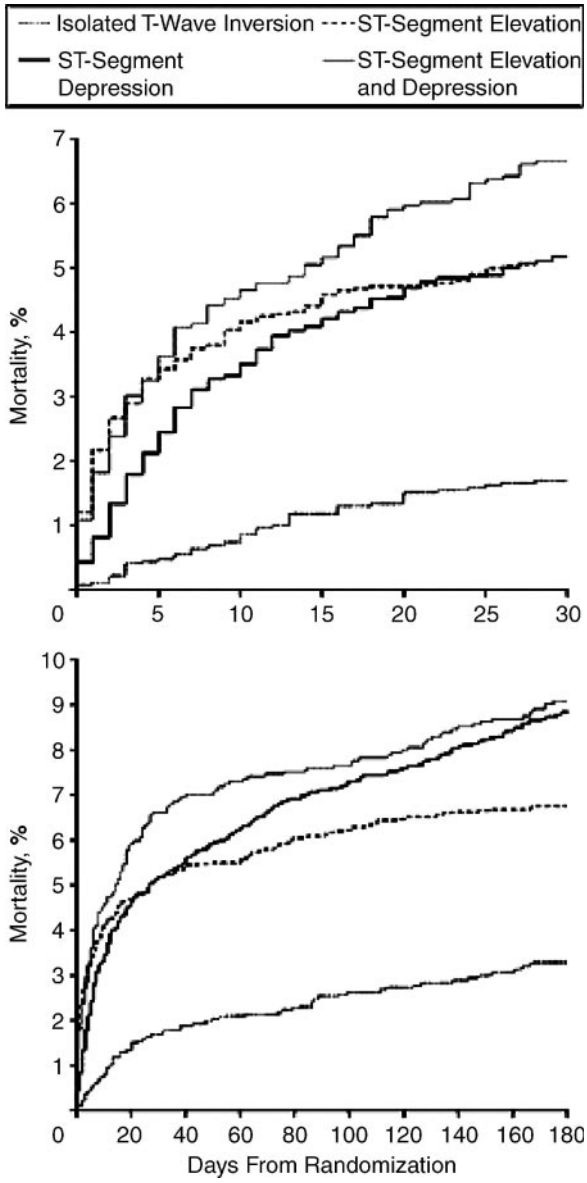

Figure 19. Kaplan-Meier Estimates of Probability of Death Based on Admission Electrocardiogram

Modified with permission from Savonitto S, Ardissino D, Granger CB, et al. Prognostic value of the admission electrocardiogram in acute coronary syndromes. JAMA 1999;281:707–13 (127). Copyright © 1999 American Medical Association.

limitation in the ability to increase coronary blood flow. This is usually the result of severe coronary artery obstruction and is associated with a high risk for an adverse outcome and/or severe angina after discharge. Unless there are contraindications to revascularization, such patients generally merit referral for early coronary angiography to direct a revascularization procedure, if appropriate. On the other hand, the attainment of a higher workload (e.g., greater than 6.5 metabolic equivalents [METS]) without evidence of ischemia (low-risk treadmill score greater than or equal to 5) (575) is

Table 19. Noninvasive Risk Stratification

High risk (greater than 3% annual mortality rate)
Severe resting LV dysfunction (LVEF less than 0.35)
High-risk treadmill score (score −11 or less)
Severe exercise LV dysfunction (exercise LVEF less than 0.35)
Stress-induced large perfusion defect (particularly if anterior)
Stress-induced multiple perfusion defects of moderate size
Large, fixed perfusion defect with LV dilation or increased lung uptake (thallium-201)
Stress-induced moderate perfusion defect with LV dilation or increased lung uptake (thallium-201)
Echocardiographic wall-motion abnormality (involving more than 2 segments) developing at low dose of dobutamine (10 mcg per kg per min or less) or at a low heart rate (less than 120 beats per min)
Stress echocardiographic evidence of extensive ischemia
Intermediate risk (1% to 3% annual mortality rate)
Mild/moderate resting LV dysfunction (LVEF = 0.35 to 0.49)
Intermediate-risk treadmill score (−11 to 5)
Stress-induced moderate perfusion defect without LV dilation or increased lung intake (thallium-201)
Limited stress echocardiographic ischemia with a wall-motion abnormality only at higher doses of dobutamine involving less than or equal to 2 segments
Low risk (less than 1% annual mortality rate)
Low-risk treadmill score (score 5 or greater)
Normal or small myocardial perfusion defect at rest or with stress*
Normal stress echocardiographic wall motion or no change of limited resting wall-motion abnormalities during stress*

*Although the published data are limited, patients with these findings will probably not be at low risk in the presence of either a high-risk treadmill score or severe resting LV dysfunction (LVEF less than 0.35). Reproduced from Table 23 in Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for the Management of Patients With Chronic Stable Angina). 2002. Available at: www.acc.org/qualityandscience/clinical/statements.htm (4).

LV = left ventricular; LVEF = left ventricular ejection fraction.

associated with functionally less severe coronary artery obstruction. Such patients have a better prognosis and can often be safely managed conservatively. Ischemia that develops at greater than 6.5 METS can be associated with severe coronary artery obstruction, but unless other high-risk markers are present (greater than 0.2-mV ST-segment depression or elevation, fall in blood pressure, ST-segment shifts in multiple leads reflecting multiple coronary regions, or prolonged ST-segment shifts [greater than 6 min] in recovery), these patients also may be safely managed conservatively (Table 20).

Table 20. Noninvasive Test Results That Predict High Risk for Adverse Outcome (Left Ventricular Imaging)

Stress Radionuclide Ventriculography	Stress Echocardiography
Exercise EF 0.50 or less	Rest EF 0.35 or less
Rest EF 0.35 or less	Wall-motion score index greater than 1
Fall in EF 0.10 or greater	

Adapted from O'Rourke RA, Chatterjee K, Dodge HT, et al. Guidelines for clinical use of cardiac radionuclide imaging, December 1986: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Cardiovascular Procedures (Subcommittee on Nuclear Imaging). J Am Coll Cardiol 1986;8:1471–83 (576); and Cheitlin MD, Alpert JS, Armstrong WF, et al. ACC/AHA guidelines for the clinical application of echocardiography. Circulation 1997;95:1686–744 (577).

EF = ejection fraction.

Table 21. Noninvasive Test Results That Predict High Risk for Adverse Outcome on Stress Radionuclide Myocardial Perfusion Imaging

Abnormal myocardial tracer distribution in more than 1 coronary artery region at rest or with stress or a large anterior defect that reperfuses
Abnormal myocardial distribution with increased lung uptake
Cardiac enlargement

Adapted from O'Rourke RA, Chatterjee K, Dodge HT, et al. Guidelines for clinical use of cardiac radionuclide imaging, December 1986: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Cardiovascular Procedures (Subcommittee on Nuclear Imaging). J Am Coll Cardiol 1986;8:1471–83 (576).

Stress radionuclide ventriculography or stress echocardiography (Table 20) provides an important alternative to exercise electrocardiography testing. Myocardial perfusion imaging with pharmacological stress (Table 21) is particularly useful in patients who are unable to exercise. The prognostic value of pharmacological stress testing appears similar to that of exercise testing with imaging, although there are few direct comparisons.

As noted earlier (Section 2.3.2.), CMR is a newer imaging modality that can effectively assess cardiac function, perfusion (e.g., with adenosine stress), and viability at the same study. The combination of these features has been reported to yield excellent predictive information in suspected CAD/ACS patients (296).

3.4.2. Noninvasive Test Selection

There are no conclusive data that either LV function or myocardial perfusion at rest and during exercise or pharmacological stress is superior in the assessment of prognosis. Both the extent of CAD and the degree of LV dysfunction are important in the selection of the appropriate therapy. Studies that directly compare prognostic information from multiple noninvasive tests for ischemia in patients after the stabilization of UA/NSTEMI are hampered by small sample size. Dobutamine stress echocardiography measures both resting LV function and the functional consequences of a coronary stenosis (571). An ischemic response is characterized by initially improved LV function at low-stress doses, followed by deterioration with increasing dobutamine doses (571). However, UA and MI are listed as contraindications for dobutamine stress echocardiography (578).

The RISC study evaluated predischarge symptom-limited bicycle exercise testing in 740 men with UA/NSTEMI (579). Multivariate analysis showed that the extent of ST-segment depression, expressed as the number of leads with ischemic changes at a low maximal workload, was negatively correlated independently with infarct-free survival rates at 1 year. This and other smaller studies permit a comparison of the effectiveness of exercise ECG with exercise or dipyridamole thallium-201 study for risk stratification. All of these noninvasive tests

show similar accuracy in dichotomization of the total population into low- and high-risk subgroups.

Selection of the noninvasive stress test should be based primarily on patient characteristics, local availability, and expertise in interpretation (580). Because of simplicity, lower cost, and widespread familiarity with performance and interpretation, the standard low-level exercise ECG stress test remains the most reasonable test in patients who are able to exercise and who have a resting ECG that is interpretable for ST-segment shifts. Patients with an ECG pattern that would interfere with interpretation of the ST segment should have an exercise test with imaging. Patients who are unable to exercise should have a pharmacological stress test with imaging. Low- and intermediate-risk patients admitted with ACS may undergo symptom-limited stress testing provided they have been asymptomatic and clinically stable for 12 to 24 h.

The optimal testing strategy in women is less well defined than in men (see Section 6.1), but there is evidence that imaging studies are superior to exercise ECG evaluation in women (580,581). Exercise testing has been reported to be less accurate for diagnosis in women. At least a portion of the lower reported accuracy derives from a lower pretest likelihood of CAD in women than in men; the higher prevalence of ischemia secondary to vascular dysfunction (coronary endothelial and/or microvascular dysfunction) in the absence of obstructive CAD also is a likely contributor to this.

Results of a symptom-limited exercise test performed 3 to 7 d after UA/NSTEMI were compared with results of a test conducted 1 month later in 189 patients (534,582). The diagnostic and prognostic values of the tests were similar, but the earlier test identified patients who developed adverse events during the first month, and this represented approximately one half of all events that occurred during the first year. These data illustrate the importance of early noninvasive testing for risk stratification.

The VANQWISH trial used symptom-limited thallium exercise treadmill testing at 3 to 5 d to direct the need for angiography in the 442 non–Q-wave MI patients randomized to an early conservative strategy (534). Among subjects in the conservative arm meeting VANQWISH stress test criteria to cross over to coronary angiography, 51% were found to have surgical CAD and showed favorable outcomes after revascularization (583). These findings support the concept that noninvasive stress testing can be used successfully to identify a high-risk subset of patients who can be directed to coronary angiography. It is unlikely that any angiographically directed early revascularization strategy could alter the very low early event rates observed in patients without a high-risk stress test.

Noninvasive tests are most useful for management decisions when risk can be stated in terms of events over time. A large population of patients must be studied to derive and test the equations needed to accurately predict individual patient risk. No noninvasive study has been reported in a sufficient number of patients after the stabilization of UA/NSTEMI to develop and test the accuracy of a multivariable equation to report test results in terms of absolute risk. Therefore, data from studies of stable angina patients must be used for risk, reported as events over time. Although the pathological process that evokes ischemia may be different in the 2 forms of angina, it is likely that the use of prognostic nomograms derived from patients with stable angina also are predictive of risk in patients with recent UA/NSTEMI after stabilization. With this untested assumption, the much larger literature derived from populations that include patients with both stable angina and UA/NSTEMI provides equations for risk stratification that convert physiological changes observed during noninvasive testing into statements of risk expressed as events over time.

3.4.3. Selection for Coronary Angiography

In contrast to the noninvasive tests, coronary angiography provides detailed structural information to allow an assessment of prognosis and to provide direction for appropriate management. When combined with LV angiography, it also allows an assessment of global and regional LV function. Indications for coronary angiography are interwoven with indications for possible therapeutic plans, such as PCI or CABG.

Coronary angiography is usually indicated in patients with UA/NSTEMI who either have recurrent symptoms or ischemia despite adequate medical therapy or are at high risk as categorized by clinical findings (HF, serious ventricular arrhythmias) or noninvasive test findings (significant LV dysfunction: ejection fraction less than 0.35, large anterior or multiple perfusion defects; Tables 19, 20, and 21), as discussed in Section 3.4.2. Patients with UA/NSTEMI who have had previous PCI or CABG also should generally be considered for early coronary angiography, unless prior coronary angiography data indicate that no further revascularization is likely to be possible. The placement of an IABP may allow coronary angiography and revascularization in those with hemodynamic instability (see Section 3.1.2.7). Patients with suspected Prinzmetal's variant angina also are candidates for coronary angiography (see Section 6.7).

In all cases, the general indications for coronary angiography and revascularization are tempered by individual patient characteristics and preferences. Patient and physician judgments regarding risks and benefits are particularly important for patients who might not be candidates for coronary revascularization, such as very frail older adults and those with serious comorbid conditions (i.e., severe hepatic, pulmonary, or renal failure; active or inoperable cancer).

3.4.4. Patient Counseling

Results of testing should be discussed with the patient, the patient's family, and/or the patient's advocate in a language that is understood by them. Test results should be used to help determine the advisability of coronary angiography, the need for adjustments in the medical regimen, and the need for secondary prevention measures (see Section 5).

4. Coronary Revascularization

4.1. Recommendations for Revascularization With PCI and CABG in Patients With UA/NSTEMI

(See Fig. 20 for details of the decision tree.)

4.1.1. Recommendations for PCI

CLASS I

1. An early invasive PCI strategy is indicated for patients with UA/NSTEMI who have no serious comorbidity and who have coronary lesions amenable to PCI and any of the high-risk features listed in Section 3.3. (See Section 3.3 for specific recommendations and their Level of Evidence.)
2. Percutaneous coronary intervention (or CABG) is recommended for UA/NSTEMI patients with 1- or 2-vessel CAD with or without significant proximal left anterior descending CAD but with a large area of viable myocardium and high-risk criteria on noninvasive testing. *(Level of Evidence: B)*
3. Percutaneous coronary intervention (or CABG) is recommended for UA/NSTEMI patients with multivessel coronary disease with suitable coronary anatomy, with normal LV function, and without diabetes mellitus. *(Level of Evidence: A)*
4. An intravenous platelet GP IIb/IIIa inhibitor is generally recommended in UA/NSTEMI patients undergoing PCI. *(Level of Evidence: A)* See Section 3.2.3 and Figures 7, 8, and 9 for details on timing and dosing recommendations (see Table 13).

CLASS IIa

1. Percutaneous coronary intervention is reasonable for focal saphenous vein graft (SVG) lesions or multiple stenoses in UA/NSTEMI patients who are undergoing medical therapy and who are poor candidates for reoperative surgery. *(Level of Evidence: C)*
2. Percutaneous coronary intervention (or CABG) is reasonable for UA/NSTEMI patients with 1- or 2-vessel CAD with or without significant proximal left anterior descending CAD but with a moderate area of viable myocardium and ischemia on noninvasive testing. *(Level of Evidence: B)*
3. Percutaneous coronary intervention (or CABG) can be beneficial compared with medical therapy for UA/NSTEMI patients with 1-vessel disease with significant proximal left anterior descending CAD. *(Level of Evidence: B)*
4. Use of PCI is reasonable in patients with UA/NSTEMI with significant left main CAD (greater than 50% diameter stenosis) who are candidates for revascularization but are not eligible for CABG or who require emergent intervention at angiography for hemodynamic instability. *(Level of Evidence: B)*

CLASS IIb

1. In the absence of high-risk features associated with UA/NSTEMI, PCI may be considered in patients with single-vessel or multivessel CAD who are undergoing medical therapy and who have 1 or more lesions to be dilated with a reduced likelihood of success. *(Level of Evidence: B)*
2. Percutaneous coronary intervention may be considered for UA/NSTEMI patients who are undergoing medical therapy who have 2- or 3-vessel disease, significant proximal left anterior descending CAD, and treated diabetes or abnormal LV function, with anatomy suitable for catheter-based therapy. *(Level of Evidence: B)*

CLASS III

1. Percutaneous coronary intervention (or CABG) is not recommended for patients with 1- or 2-vessel CAD without significant proximal left anterior descending CAD with no current symptoms or symptoms that are unlikely to be due to myocardial ischemia and who have no ischemia on noninvasive testing. *(Level of Evidence: C)*
2. In the absence of high-risk features associated with UA/NSTEMI, PCI is not recommended for patients with UA/NSTEMI who have single-vessel or multivessel CAD and no trial of medical therapy, or who have 1 or more of the following:
   a. Only a small area of myocardium at risk. *(Level of Evidence: C)*
   b. All lesions or the culprit lesion to be dilated with morphology that conveys a low likelihood of success. *(Level of Evidence: C)*
   c. A high risk of procedure-related morbidity or mortality. *(Level of Evidence: C)*
   d. Insignificant disease (less than 50% coronary stenosis). *(Level of Evidence: C)*
   e. Significant left main CAD and candidacy for CABG. *(Level of Evidence: B)*
3. A PCI strategy in stable patients with persistently occluded infarct-related coronary arteries after NSTEMI is not indicated. *(Level of Evidence: B)*

4.1.2. Recommendations for CABG

CLASS I

1. Coronary artery bypass graft surgery is recommended for UA/NSTEMI patients with significant left main CAD (greater than 50% stenosis). *(Level of Evidence: A)*
2. Coronary artery bypass graft surgery is recommended for UA/NSTEMI patients with 3-vessel disease; the survival benefit is greater in patients with abnormal LV function (LVEF less than 0.50). *(Level of Evidence: A)*
3. Coronary artery bypass graft surgery is recommended for UA/NSTEMI patients with 2-vessel disease with significant proximal left anterior descending CAD and either abnormal LV function (LVEF less than 0.50) or ischemia on noninvasive testing. *(Level of Evidence: A)*
4. Coronary artery bypass graft surgery is recommended for UA/NSTEMI patients in whom percutaneous revascularization is not optimal or possible and who have ongoing ischemia not responsive to maximal nonsurgical therapy. *(Level of Evidence: B)*
5. Coronary artery bypass graft surgery (or PCI) is recommended for UA/NSTEMI patients with 1- or 2-vessel CAD with or without significant proximal left anterior descending CAD but with a large area of viable myocardium and high-risk criteria on noninvasive testing. *(Level of Evidence: B)*
6. Coronary artery bypass graft surgery (or PCI) is recommended for UA/NSTEMI patients with multivessel coronary disease with suitable coronary anatomy, with normal LV function, and without diabetes mellitus. *(Level of Evidence: A)*

CLASS IIa

1. For patients with UA/NSTEMI and multivessel disease, CABG with use of the internal mammary arteries can be beneficial over PCI in patients being treated for diabetes. *(Level of Evidence: B)*
2. It is reasonable to perform CABG with the internal mammary artery for UA/NSTEMI patients with multivessel disease and treated diabetes mellitus. *(Level of Evidence: B)*

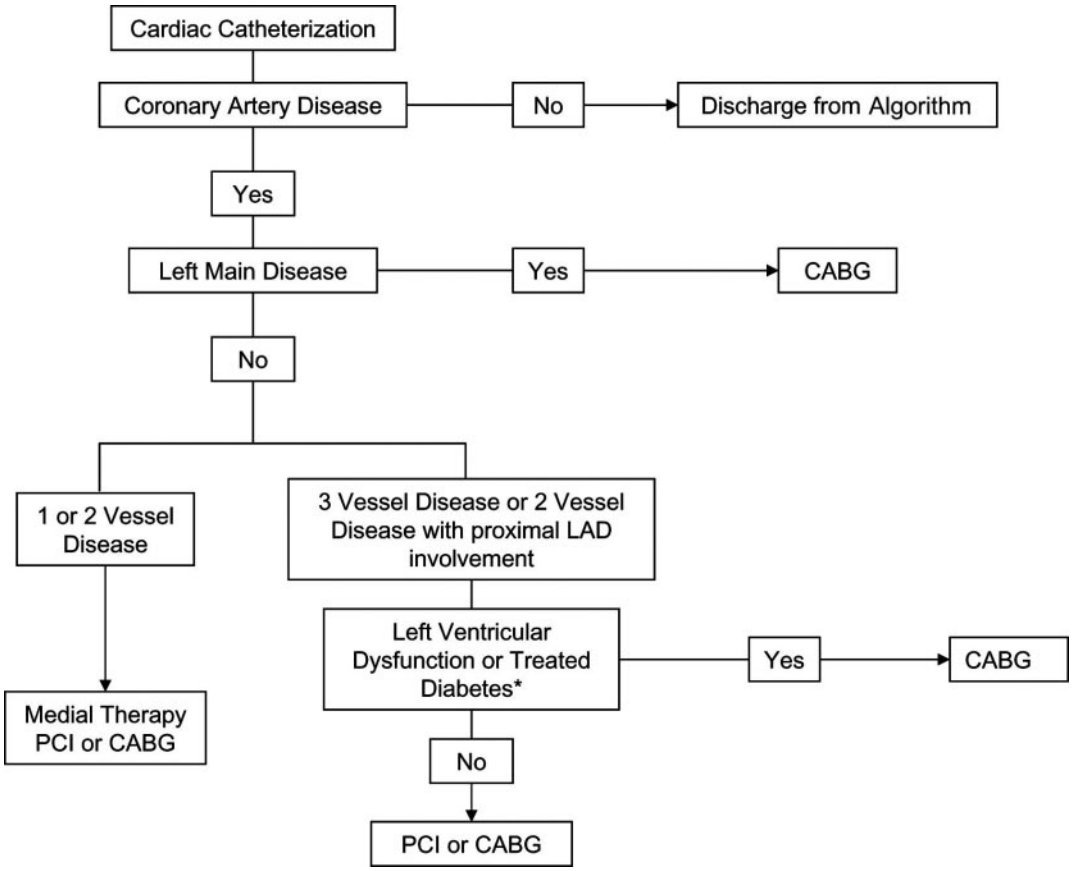

Figure 20. Revascularization Strategy in UA/NSTEMI

*There is conflicting information about these patients. Most consider CABG to be preferable to PCI. CABG = coronary artery bypass graft; LAD = left anterior descending coronary artery; PCI = percutaneous coronary intervention UA/NSTEMI = unstable angina/non–ST-elevation myocardial infarction.

3. Repeat CABG is reasonable for UA/NSTEMI patients with multiple SVG stenoses, especially when there is significant stenosis of a graft that supplies the LAD. *(Level of Evidence: C)*
4. Coronary artery bypass graft surgery (or PCI) is reasonable for UA/NSTEMI patients with 1- or 2-vessel CAD with or without significant proximal left anterior descending CAD but with a moderate area of viable myocardium and ischemia on noninvasive testing. *(Level of Evidence: B)*
5. Coronary artery bypass graft surgery (or PCI) can be beneficial compared with medical therapy for UA/NSTEMI patients with 1-vessel disease with significant proximal left anterior descending CAD. *(Level of Evidence: B)*
6. Coronary artery bypass surgery (or PCI with stenting) is reasonable for patients with multivessel disease and symptomatic myocardial ischemia. *(Level of Evidence: B)*

CLASS IIb

Coronary artery bypass graft surgery may be considered in patients with UA/NSTEMI who have 1- or 2-vessel disease not involving the proximal LAD with a modest area of ischemic myocardium when percutaneous revascularization is not optimal or possible. (If there is a large area of viable myocardium and high-risk criteria on noninvasive testing, this recommendation becomes a Class I recommendation.) *(Level of Evidence: B)*

CLASS III

Coronary artery bypass graft surgery (or PCI) is not recommended for patients with 1- or 2-vessel CAD without significant proximal left anterior descending CAD with no current symptoms or symptoms that are unlikely to be due to myocardial ischemia and who have no ischemia on noninvasive testing. *(Level of Evidence: C)*

4.2. General Principles

As discussed in Section 3.4.3, coronary angiography is useful for defining the coronary artery anatomy in patients with UA/NSTEMI and for identifying subsets of high-risk patients who can benefit from early revascularization. Coronary revascularization (PCI or CABG) is performed to improve prognosis, relieve symptoms, prevent ischemic complications, and improve functional capacity. The decision to proceed from diagnostic angiography to revascularization is influenced not only by the coronary anatomy but also by a number of additional factors, including anticipated life expectancy, ventricular function, comorbidity, functional capacity, severity of symptoms, and quantity of viable myocardium at risk. These are all important variables that must be considered before revascularization is recommended. For example, patients with distal obstructive cor-

onary lesions or those who have large quantities of irreversibly damaged myocardium are unlikely to benefit from revascularization, particularly if they can be stabilized with medical therapy. Patients with high-risk coronary anatomy are likely to benefit from revascularization in terms of both symptom improvement and long-term survival (Fig. 20). The indications for coronary revascularization in patients with UA/NSTEMI are similar to those for patients with chronic stable angina and are presented in greater detail in the ACC/AHA Guidelines for the Management of Patients With Chronic Stable Angina (4), the ACC/AHA Guidelines for Coronary Artery Bypass Graft Surgery (555), and the 2005 ACC/AHA/SCAI Guidelines Update for Percutaneous Coronary Intervention (2).

Plaque rupture with subsequent platelet aggregation and thrombus formation is most often the underlying pathophysiological cause of UA/NSTEMI (124,126). The management of many patients with UA/NSTEMI often involves revascularization of the underlying CAD with either PCI or CABG. Selection of the appropriate revascularization strategy depends on clinical factors, operator experience, and extent of the underlying CAD. Many patients with UA/NSTEMI have coronary disease that is amenable to either form of therapy; however, some patients have high-risk features, such as reduced LV function, that place them in a group of patients who experience improved long-term survival rates with CABG. In other patients, adequate revascularization with PCI might not be optimal or even possible, and CABG would be the better revascularization choice. In still other patients who are poor surgical candidates, PCI is preferred.

Findings in large registries of patients with CAD suggest that the mode of clinical presentation should have little bearing on the subsequent revascularization strategy (7,9,13,124,126). In a series of 9,263 patients with CAD, an admission diagnosis of UA (vs. chronic stable angina) had no influence on 5-year survival rates after CABG, percutaneous transluminal coronary angioplasty (PTCA), or medical treatment (584). An initial diagnosis of UA also did not influence survival 3 years after either CABG or PTCA in 59,576 patients treated in the state of New York (585). Moreover, long-term survival rates after CABG are similar for UA patients who present with rest angina, increasing angina, new-onset angina, or post-MI angina (586). These observations suggest that published data that compare definitive treatments for patients who initially present with multiple clinical manifestations of CAD can be used to guide management decisions for patients who present with UA/NSTEMI. Consequently, the indications for coronary revascularization in patients with UA/NSTEMI are, in general, similar to those for patients with stable angina. The principal difference is that the impetus for some form of revascularization is stronger in patients with UA/NSTEMI by the very nature of the presenting symptoms (586). Moreover, revascularization in patients with UA/NSTEMI, particularly those with high-risk characteristics, appears to be of most benefit if performed early in the hospital course (see Section 3.3).

4.3. Percutaneous Coronary Intervention

In recent years, technological advances coupled with high acute success rates and low complication rates have increased the use of percutaneous catheterization in patients with UA/NSTEMI. Stenting and the use of adjunctive platelet GP IIb/IIIa inhibitors have further broadened the use of PCI by improving both the safety and durability of these procedures. Percutaneous coronary revascularization (intervention) strategies are referred to in these guidelines as "PCI." This term refers to a family of percutaneous techniques, including standard balloon angioplasty (PTCA), intracoronary stenting, and atheroablative technologies (e.g., atherectomy, thrombectomy, or laser angioplasty). "Percutaneous transluminal coronary angioplasty" sometimes is used to refer to studies in which this was the dominant form of PCI, before the widespread use of stenting. The majority of current PCIs involve balloon dilation and coronary stenting. Stenting has contributed greatly to catheter-based revascularization by reducing the risks of both acute vessel closure and late restenosis. Drug-eluting stents have been demonstrated to markedly reduce the risk of restenosis compared with bare-metal stents. Although stenting has become the most widely used percutaneous technique, with most laboratories in the United States employing stents in 80% to 85% of their PCI procedures, other devices continue to be used for specific lesions and patient subsets. Although the technical safety and efficacy of atheroablative and thrombectomy devices have been described, few data exist to demonstrate incremental benefit with regard to clinical outcomes, and even less information is available that describes the use of these strategies specifically in patients with UA/NSTEMI (587). The need to continue with the development of safer, more effective PCI techniques is emphasized by recently raised concerns about delayed endothelialization over DES and consequent increases in late coronary thrombotic events, potentially leading to death or MI (399,400,402,403,411).

Other techniques and devices, such as the AngioJet thrombectomy catheter, have been tested for the treatment of thrombi that are visible within a coronary artery (588). Experience with these devices has indicated that the angiographic appearance of a coronary stenosis can be improved, but few comparative data exist to substantiate improvements in clinical outcome.

The reported clinical efficacy of PCI in UA/NSTEMI has varied. This is likely attributable to differences in study design, treatment strategies, patient selection, and operator experience. Nevertheless, the success rate of PCI in patients with UA/NSTEMI overall is quite high. In TIMI IIIB, for example, angiographic success was achieved in 96% of patients with UA/NSTEMI who underwent balloon angioplasty. With clinical criteria, periprocedural MI occurred in 2.7% of patients, emergency CABG surgery was required in

1.4% of patients, and the death rate due to the procedure was 0.5% (129,589).

The use of balloon angioplasty has been evaluated in several other trials of patients with UA versus stable angina (590–595). A large retrospective study compared the results of angioplasty in patients with stable angina to that in patients with UA (591). After an effort to manage patients with UA with medical therapy, PTCA was performed an average of 15 d after hospital admission. Compared with patients with stable angina, UA patients showed no significant differences with respect to primary clinical success (92% for UA vs. 94% for stable angina), in-hospital mortality rates (0.3% vs. 0.1%), or the number of adverse events at 6-month follow-up (591). These findings suggest that results in immediate and 6-month outcomes are comparable in patients with stable angina and UA. In addition, in a retrospective analysis, the results in UA patients were similar regardless of whether the procedure was performed early (less than 48 h) or late (greater than 48 h) after hospital presentation (590).

Although other earlier studies (predominantly from the 1980s) had suggested that patients with UA who undergo balloon PTCA have higher rates of MI and restenosis than patients with stable angina (592–596), contemporary catheter revascularization differs by often involving coronary stenting, DES, and adjunctive use of platelet GP IIb/IIIa receptor inhibitors, which are likely to affect not only immediate- but also long-term outcomes (512). Historically, PTCA had been limited by acute vessel closure, which occurs in approximately 5% of patients, and by coronary restenosis, which occurred in approximately 35% to 45% of treated lesions during a 6-month period. Coronary stenting has offered an important alternative to PTCA because of its association with both a marked reduction in acute closure and lower rates of restenosis. By preventing acute or threatened closure, stenting reduces the incidence of procedure-related STEMI and need for emergency CABG surgery and can also prevent other ischemic complications.

In a comparison of the use of the Palmaz-Schatz coronary stent in patients with stable angina and patients with UA, no significant differences were found with respect to in-hospital outcome or restenosis rates (597). Another study found similar rates of initial angiographic success and in-hospital major complications in stented patients with UA compared with those with stable angina (598). Major adverse cardiac events at 6 months were also similar between the 2 groups, whereas the need for repeat PCI and target-vessel revascularization was actually less in the UA group. On the other hand, other data have suggested that UA increases the incidence of adverse ischemic outcomes in patients undergoing coronary stent deployment despite therapy with ticlopidine and ASA, which suggests the need for more potent antiplatelet therapy in this patient population (599).

Drug-eluting stent use for UA/NSTEMI has increased dramatically in recent years. Kandzari et al. evaluated patterns of DES utilization in 8,852 high-risk UA/NSTEMI patients who underwent PCI between 2003 and 2004 in 262 hospitals in the CRUSADE Quality Improvement Initiative (601). During a 9-month period, DES use increased from 52.6% to 78.5% of cases. Differences in selection of DES compared with bare bare-metal stents were noted, but adjusted rates of death and recurrent infarction were favorable for DES.

The open artery hypothesis suggested that late patency of an infarct artery is associated with improved LV function, increased electrical stability, and the provision of collateral vessels to other coronary beds for protection against future events. The Occluded Artery Trial (OAT) (602, 603) tested the hypothesis that routine PCI for total occlusion 3 to 28 d after MI would reduce the composite of death, reinfarction, or Class IV heart failure. Stable patients (n = 2166) with an occluded infarct artery after MI were randomized to optimal medical therapy and PCI with stenting or optimal medical therapy alone. The qualifying period of 3 to 28 d was based on calendar days, thus the minimal time from symptom onset to angiography was just over 24 h. Inclusion criteria included absence of angina or heart failure at rest and LVEF less than 50% or proximal occlusion of a major epicardial artery with a large risk region. Exclusion criteria included NYHA Class III or IV heart failure, serum creatinine greater than 2.5 mg/dL, left main or 3-vessel disease, clinical instability, or severe inducible ischemia on stress testing if the infarct zone was not akinetic or dyskinetic.

Percutaneous coronary intervention did not reduce death, reinfarction, or HF, and there was a trend toward excess reinfarction during 4 years of follow-up. Findings in the 295-patient NSTEMI subgroup were similar to those in the overall group (n = 2,166) and the larger STEMI groups. Thus, a routine PCI strategy in OAT-type patients with persistently occluded infarct-related coronary arteries after NSTEMI is not indicated.

4.3.1. Platelet Inhibitors and Percutaneous Revascularization

An important advance in the treatment of patients with UA/NSTEMI who are undergoing PCI was the introduction of platelet GP IIb/IIIa receptor inhibitors in the 1990s (see Section 3.2) (126,128,130,510–512,604–606). This therapy takes advantage of the fact that platelets play an important role in the development of ischemic complications that can occur in patients with UA/NSTEMI or during coronary revascularization procedures. Currently, 3 platelet GP IIb/IIIa inhibitors are approved by the Food and Drug Administration on the basis of the outcomes of a variety of placebo-controlled clinical trials: abciximab, tirofiban, and eptifibatide. The EPIC (510), EPILOG (511), CAPTURE (372), and EPISTENT (512) trials investigated the use of abciximab; the PRISM (374), PRISM-PLUS (130), and Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis (RESTORE) (518) trials evaluated tirofiban; and the Integrilin to Minimize Platelet

Aggregation and Coronary Thrombosis (IMPACT) (517), PURSUIT (128), and Enhanced Suppression of Platelet Receptor GP IIb/IIIa using Integrilin Therapy (ESPRIT) (519) trials studied the use of eptifibatide (Table 18). All 3 of these agents interfere with the final common pathway for platelet aggregation. All have shown efficacy in reducing the incidence of ischemic complications in patients with UA/NSTEMI (Fig. 16).

In the only head-to-head comparison of 2 GP IIb/IIIa inhibitors, the TARGET trial randomized 5,308 patients to tirofiban or abciximab before undergoing PCI with the intent to perform stenting (515). The primary end point, a composite of death, nonfatal MI, or urgent target-vessel revascularization at 30 d, occurred less frequently in those receiving abciximab than in those given tirofiban (6.0% vs. 7.6%, $p = 0.038$). There was a similar direction and magnitude for each component of the end point. Differences in outcome between the 2 randomized treatment groups were particularly marked among patients with UA/NSTEMI (63% of patients), in whom 30-d composite end point event rates were 9.3% with tirofiban versus 6.3% with abciximab ($p = 0.002$). Although this finding is subject to the limitations of subgroup analysis, it suggests that any differences in efficacy between GP IIb/IIIa inhibitors might be most apparent among patients undergoing PCI in the setting of UA/NSTEMI. Inferior efficacy observed with tirofiban in this trial might have been related to inadequate initial (loading) dosing, which was subsequently demonstrated to result in platelet inhibition that was inadequate (only 28% to 33% early platelet inhibition) and less than that achieved with abciximab (65% to 81%) (516). A subsequent study evaluating a higher bolus dose of tirofiban (25 mcg per kg) during PCI was unfortunately discontinued prematurely because of funding issues. Eptifibatide has not been compared directly to either abciximab or tirofiban.

The question of whether GP IIb/IIIa inhibition is still useful in UA/NSTEMI patients undergoing PCI who have received a high loading dose (600 mg) of clopidogrel was raised by a study in CAD patients treated in an elective setting (607). To address this, 2,022 patients with UA/NSTEMI undergoing PCI were loaded with clopidogrel, 600 mg, at least 2 h before the procedure and then randomized to receive either abciximab or placebo (ISAR-REACT 2) (244). The primary end point of death, nonfatal reinfarction, or urgent target-vessel revascularization within 30 d was reached in 8.9% of patients assigned to abciximab versus 11.9% assigned to placebo, a 25% difference, and was limited entirely to patients with an elevated troponin level, in whom the incidence of a primary event was 13.1% in the abciximab group compared with 18.3% in the placebo group ($p = 0.02$). Bleeding risks were similar in the 2 groups. Thus, GP IIb/IIIa inhibition provides incremental benefit beyond high-oral-dose clopidogrel loading for NSTEMI patients with elevated cardiac biomarker levels but not for UA patients with normal levels who are undergoing PCI.

In summary, data from both retrospective observations and randomized clinical trials indicate that PCI can lead to angiographic success in most patients with UA/NSTEMI (Table 18). The safety of these procedures in these patients is enhanced by the addition of intravenous platelet GP IIb/IIIa receptor inhibitors to the standard regimen of ASA, anticoagulants, clopidogrel, and anti-ischemic medications.

4.4. Surgical Revascularization

A meta-analysis of 6 trials conducted during the early years of CABG (between 1972 and 1978) documented a clear survival advantage for CABG over medical therapy in symptomatic patients with left main and 3-vessel coronary disease that was independent of LV function (322). No survival difference was documented between the 2 therapies for patients with 1- or 2-vessel coronary disease. However, dramatic changes in both surgical technique (including internal thoracic artery grafting to the LAD) and in medical therapy (e.g., potent anticoagulant and antiplatelet therapies) have subsequently occurred. Pocock et al. (608) performed a meta-analysis on the results of 8 randomized trials completed between 1986 and 1993 and compared the outcomes of CABG and PTCA in 3,371 patients with multivessel CAD before widespread stent use. Many of these patients presented with UA. At 1-year follow-up, no difference was documented between the 2 therapies in cardiac death or MI, but a lower incidence of angina and need for revascularization was associated with CABG.

The Bypass Angioplasty Revascularization Investigation (BARI) trial, the largest randomized comparison of CABG and PTCA, was performed in 1,829 patients with 2- or 3-vessel CAD (609,610). Unstable angina was the admitting diagnosis in 64% of these patients, and 19% had treated diabetes mellitus. A statistically significant advantage in survival without MI independent of the severity of presenting symptoms was observed for CABG over PCI at 7 years (84.4% vs. 80.9%, $p = 0.04$) (611). Subgroup analysis demonstrated that the survival benefit was confined to patients with treated diabetes mellitus (76.4% with CABG compared with 55.7% for patients treated with PTCA, $p = 0.001$). The Coronary Angioplasty versus Bypass Revascularization Investigation (CABRI) trial also showed a survival benefit for CABG in patients with diabetes mellitus with multivessel CAD (612). A confirmatory study from Emory University showed that with correction for baseline differences, patients requiring insulin with multivessel disease had improved survival with CABG versus PTCA (613) (see Section 6.2).

A large patient registry of consecutive CAD compared the 5-year survival rates for medical treatment, PTCA, and CABG between 1984 and 1990 (584). Patients with 3- or 2-vessel disease with a proximal severe (greater than or equal to 95%) LAD stenosis treated with CABG had significantly better 5-year survival rates than did those who received medical treatment or PTCA. In patients with less severe 2-vessel CAD or with 1-vessel CAD, either form of

revascularization improved survival relative to medical therapy. The 2 revascularization treatments were equivalent for patients with nonsevere 2-vessel disease. Percutaneous transluminal coronary angioplasty provided better survival rates than CABG in patients with 1-vessel disease, except for those with severe proximal LAD stenosis, for whom the 2 revascularization strategies were equivalent. However, in patients with single-vessel disease, all therapies were associated with high 5-year survival rates, and the differences among the treatment groups were very small.

Hannan et al. (585) compared 3-year risk-adjusted survival rates in 29,646 CABG patients and 29,930 PTCA patients undergoing revascularization in the state of New York in 1993, adjusted for differences in baseline and angiographic characteristics. The anatomic extent of disease was the only variable that interacted with the specific revascularization therapy that influenced long-term survival. Unstable angina or diabetes mellitus did not result in treatment-related differences in long-term survival rates. Patients with single-vessel disease not involving the LAD or with less than 70% LAD stenosis had higher adjusted 3-year survival rates with PTCA (95.3%) than with CABG (92.4%). Patients with proximal LAD stenosis of at least 70% had higher adjusted 3-year survival rates with CABG than with PTCA regardless of the number of diseased coronary vessels. Patients with 3-vessel disease had higher adjusted 3-year survival rates with CABG regardless of proximal LAD disease. Patients with other 1- or 2-vessel disease had no treatment-related difference in survival rates. The 3-year reintervention rate was significantly higher in the PCI group than in the CABG group both for subsequent CABG (10.4% vs. 0.5%) and for subsequent PCI (26.6% vs. 2.8%).

Hannan et al. performed a follow-up study using the same New York State cardiac registries to compare the outcomes of 37,212 patients who underwent CABG with 22,102 patients who underwent PCI using stents (614). The maximum follow-up was more than 3 years in each group. Patients were divided into 5 anatomic groups; 2-vessel disease without LAD disease; 2-vessel disease with proximal LAD disease; 2-vessel disease with nonproximal LAD disease; 3-vessel disease with proximal LAD disease; and 3-vessel disease with nonproximal LAD disease. Patients with single-vessel disease were generally treated with PCI. The unanticipated finding was that the risk-adjusted long-term mortality of patients in all 5 subsets was lower in the CABG group. The HR for death after CABG compared with stent implantation ranged from a low of 0.64 (95% CI 0.56 to 0.74) for patients with 3-vessel disease and proximal LAD disease to a high of 0.76 (95% CI 0.60 to 0.96) for patients with 2-vessel disease with involvement of the nonproximal LAD. The risk of long-term mortality also was lower with CABG for patients with diabetes in each of these anatomic subsets, with HRs ranging from 0.59 to 0.69. In all but the subset of patients with 2-vessel disease without LAD disease, the increase in mortality associated with PCI compared with CABG was significant for patients with diabetes. The lack of significance in this subset likely reflected smaller numbers of patients (CABG plus PCI combined). In this study (614), as in the earlier study by Hannan et al. (585), the 3-year reintervention rate was significantly higher in the PCI group than in the CABG group for both subsequent CABG (7.8% vs. 0.3%) and subsequent PCI (27.3% vs. 4.6%). In contrast, the randomized trials of multivessel disease have shown no differences in patients without diabetes. These disparate results could be due to adverse selection biases for PCI. On the other hand, the registry is very large and included a broad range of angiographic characteristics not included in the randomized trials. Consistently, however, the location of a coronary stenosis in the LAD, especially if severe and proximal, is a characteristic associated with higher mortality rates and with a favorable outcome with CABG.

The BARI and CABRI randomized trials appeared to identify a subset of diabetic patients who had a better outcome with CABG than with PTCA, a finding not observed in earlier cohort studies (609,610,612) but confirmed in a more recent cohort study that exclusively used stents in the PCI group (614). Analysis of the subgroup with diabetes was retrospective in both the BARI and CABRI trials. Moreover, the treatment-related effect was not reproduced in the BARI registry population (615). A reasonable explanation for these inconsistent results is that physicians might be able to recognize characteristics of CAD in diabetic patients that permit patients to more safely undergo one or the other revascularization therapy. However, when all patients with diabetes are randomly assigned to therapies without the added insight of clinical judgment, a treatment advantage is apparent for CABG. Given the combination of data derived from randomized trials and more recent cohort studies comparing PCI using stents with CABG, it is reasonable to consider CABG as the preferred revascularization strategy for most patients with 3-vessel disease, especially if it involves the proximal LAD, and for patients with multivessel disease and treated diabetes mellitus or LV dysfunction. Alternatively, it would be unwise to deny the advantages of PCI to a patient with diabetes and less severe coronary disease on the basis of the current information. In addition, the use of GP IIb/IIIa inhibitors together with PCI for UA/NSTEMI in recent years appears to have resulted in more favorable outcomes (133,616).

An important consideration in a comparison of different revascularization strategies is that none of the large randomized trials reflect the current practice of interventional cardiology that includes the routine use of stents, with an increasing use of DES, and the increasing use of platelet receptor inhibitors. Coronary stenting improves procedural safety, and DES reduce restenosis compared with PTCA or bare-metal stents. The adjuvant use of platelet inhibitors, particularly in high-risk patients, is also associated with improved short- and intermediate-term outcomes. Although the effects of DES and platelet GP IIb/IIIa inhib-

itors could have improved the PCI results observed, their added benefit relative to CABG cannot be assumed or assessed on the basis of the previously reported randomized trials or large registries. Meanwhile, refinement of surgical management with right internal mammary artery grafts, radial artery grafts, improved myocardial protection strategies, and less invasive methodology could have reduced the morbidity and mortality rates for CABG. In fact, the risk-adjusted mortality for CABG has declined progressively during the last decade based on data derived from the STS National Adult Cardiac Database (617).

The most recent comparisons of PCI and CABG surgery, relevant to current medical practice, can be summarized as follows: In a randomized study of patients with medically refractory myocardial ischemia at high risk of adverse outcomes of CABG surgery (the Angina With Extremely Serious Operative Mortality Evaluation [AWESOME] trial), there was comparable survival with traditional CABG surgery and PCI, which included stenting or atherectomy (618). A meta-analysis of CABG versus stenting for the treatment of multivessel disease (619) included patients in the randomized trials Arterial Revascularization Therapy Study (ARTS), Stent or Surgery (SoS), Estudio Randomizado Argentino de Angioplastia vs. CIrugia-II (ERACI-II), and Multicenter Anti Atherosclerotic Study-II (MASS-II) (620–624). ERACI-II included a cohort in which 92% of the patients had UA; patients in the SoS study did not have apparent recent acute events; patients in MASS-II had stable angina and preserved ventricular function; and those in ARTS (with 5-year follow-up data) were not specifically described. However, these trials, which enrolled patients between 1995 and 2000 and primarily used traditional on-pump CABG surgery and PCI with bare-metal stents, showed no difference in the primary composite end point of death, MI, and stroke and no difference in mortality between the CABG and the stent groups. The ARTS trial, which included but was not limited to patients with UA, randomized patients with multivessel disease to coronary stenting versus CABG. Three-year survival rates without stroke and MI were identical in both groups.

Nevertheless, evolutionary changes in revascularization therapy require randomized trials that incorporate the most contemporary therapies. Off-pump CABG and PCI with DES are 2 examples. Indeed, not all evolutionary changes in therapy have shown net incremental clinical benefits. Randomized trial data suggest that coronary graft patency rates are somewhat lower with off-pump CABG (625). The use of DES has not decreased the occurrence of death or MI compared with bare-metal stents, and DES are subject to a small increase in the rate of late (greater than 6-month, off-dual-platelet antagonism) stent thrombotic complications and thrombosis-related clinical events (399,400,402, 403,411,626). Further complicating the picture, ASA and clopidogrel and other medical therapies are increasingly utilized in patients after CABG (627), which makes comparisons of medical, PCI, and surgical therapy challenging. The requirement for long-term follow-up and the need for adequate statistical power add to the difficulty in defining the unique benefits of each of the available forms of therapy separately. In summary, it cannot be assumed that all evolutionary changes in these therapies will have a beneficial impact on long-term outcomes, and clinical judgment in treatment selection for individual patients and a conservative approach to new therapies are indicated.

4.5. Conclusions

In general, the indications for PCI and CABG in UA/NSTEMI are similar to those for stable angina (628–633). High-risk patients with LV systolic dysfunction, patients with diabetes mellitus, and those with 2-vessel disease with severe proximal LAD involvement or severe 3-vessel or left main disease should be considered for CABG (Fig. 20). Many other patients will have less severe CAD that does not put them at high risk for cardiac death. However, even less severe disease can have a substantial negative impact on the quality of life. Compared with high-risk patients, low-risk patients will have negligibly increased chances of long-term survival with CABG (or PCI) and therefore should be managed medically. However, in low-risk patients, quality of life and patient preferences may be considered in addition to strict clinical outcomes in the selection of a treatment strategy. Low-risk patients whose symptoms do not respond well to maximal medical therapy and who experience a significant negative impact on their quality of life and functional status should be considered for revascularization. Patients in this group who are unwilling to accept the increased short-term procedural risks to gain long-term benefits or who are satisfied with their existing capabilities should be managed medically at first and followed up carefully as outpatients. Other patients who are willing to accept the risks of revascularization and who want to improve their functional status or to decrease symptoms may be considered appropriate candidates for early revascularization.

5. Late Hospital Care, Hospital Discharge, and Post-Hospital Discharge Care

The acute phase of UA/NSTEMI is usually over within 2 months. The risk of progression to MI or the development of recurrent MI or death is highest during that period. At 1 to 3 months after the acute phase, most patients resume a clinical course similar to that in patients with chronic stable coronary disease.

The broad goals during the hospital discharge phase are 2-fold: 1) to prepare the patient for normal activities to the extent possible and 2) to use the acute event as an opportunity to reevaluate the plan of care, particularly lifestyle and risk factor modification. Aggressive risk factor modifications that can prolong survival should be the main goals of long-term management of stable CAD. Patients who have undergone successful PCI with an uncomplicated course are usually discharged the next day,

and patients who undergo uncomplicated CABG are generally discharged 4 to 7 d after CABG. Medical management of low-risk patients after noninvasive stress testing and coronary angiography can typically be accomplished rapidly, with discharge soon after testing. Medical management of a high-risk group of patients who are unsuitable for or unwilling to undergo revascularization could require vigilant inpatient monitoring in order to achieve adequate ischemic symptom control with medical therapy that will minimize future morbidity and mortality and improve quality of life.

5.1. Medical Regimen and Use of Medications

RECOMMENDATIONS

CLASS I

1. **Medications required in the hospital to control ischemia should be continued after hospital discharge in patients with UA/NSTEMI who do not undergo coronary revascularization, patients with unsuccessful revascularization, and patients with recurrent symptoms after revascularization. Upward or downward titration of the doses may be required. *(Level of Evidence: C)***
2. **All post-UA/NSTEMI patients should be given sublingual or spray NTG and instructed in its use. *(Level of Evidence: C)***
3. **Before hospital discharge, patients with UA/NSTEMI should be informed about symptoms of worsening myocardial ischemia and MI and should be instructed in how and when to seek emergency care and assistance if such symptoms occur. *(Level of Evidence: C)***
4. **Before hospital discharge, post-UA/NSTEMI patients and/or designated responsible caregivers should be provided with supportable, easily understood, and culturally sensitive instructions with respect to medication type, purpose, dose, frequency, and pertinent side effects. *(Level of Evidence: C)***
5. **In post-UA/NSTEMI patients, anginal discomfort lasting more than 2 or 3 min should prompt the patient to discontinue physical activity or remove himself or herself from any stressful event. If pain does not subside immediately, the patient should be instructed to take 1 dose of NTG sublingually. If the chest discomfort/pain is unimproved or worsening 5 min after 1 NTG dose has been taken, it is recommended that the patient or a family member/friend call 9-1-1 immediately to access EMS. While activating EMS access, additional NTG (at 5-min intervals 2 times) may be taken while lying down or sitting. *(Level of Evidence: C)***
6. **If the pattern or severity of anginal symptoms changes, which suggests worsening myocardial ischemia (e.g., pain is more frequent or severe or is precipitated by less effort or now occurs at rest), the patient should contact his or her physician without delay to assess the need for additional treatment or testing. *(Level of Evidence: C)***

In most cases, the inpatient anti-ischemic medical regimen used in the nonintensive phase (other than intravenous NTG) should be continued after discharge, and the antiplatelet/anticoagulant medications should be changed to an outpatient regimen. The goals for continued medical therapy after discharge relate to potential prognostic benefits (primarily shown for antiplatelet agents, beta blockers, low-density cholesterol (LDL-C)-lowering agents, and inhibitors of the renin-angiotensin aldosterone system, especially for ejection fraction of 0.40 or less), control of ischemic symptoms (nitrates, beta blockers, and CCBs), and treatment of major risk factors such as hypertension, smoking, dyslipidemia, physical inactivity, and diabetes mellitus (see Section 5.2). Thus, the selection of a medical regimen is individualized to the specific needs of each patient based on the in-hospital findings and events, the risk factors for CAD, drug tolerability, and recent procedural interventions. The mnemonic ABCDE (Aspirin, antianginals, and ACE inhibitors; Beta blockers and blood pressure; Cholesterol and cigarettes; Diet and diabetes; Education and exercise) has been found to be useful in guiding treatment (4,634).

An effort by the entire multidisciplinary team with special skills (physicians, nurses, dietitians, pharmacists, rehabilitation specialists, care managers, and physical and occupational therapists) is often necessary to prepare the patient for discharge. Both the patient and family should receive instructions about what to do if ischemic symptoms occur in the future (74). Face-to-face patient instruction is important and should be reinforced and documented with written instruction sheets. Enrollment in a cardiac rehabilitation program after discharge can enhance patient education and compliance with the medical regimen (see Section 5.4).

Telephone follow-up can serve to reinforce in-hospital instruction, provide reassurance, and answer the patient's questions (635). If personnel and budget resources are available, the health care team should establish a follow-up system in which personnel specially trained to support and assist clinicians in CAD management call patients on the telephone. For example, calls might occur weekly for the first 4 weeks after discharge. This structured program can gauge the progress of the patient's recovery, reinforce the CAD education taught in the hospital, address patient questions and concerns, and monitor progress in meeting risk factor modification goals.

5.2. Long-Term Medical Therapy and Secondary Prevention

Patients with UA/NSTEMI require secondary prevention for CAD at discharge. The management of the patient with stable CAD is of relevance, as detailed in the ACC/AHA/ACP Guidelines for the Management of Patients With Chronic Stable Angina (4), as are the secondary prevention guidelines (3) outlined in the more recent ACC/AHA Guidelines for the Management of Patients With ST-Elevation MI (1) and Secondary Prevention (3,38).

A health care team with expertise in aggressively managing CAD risk factors should work with patients and their families to educate them in detail regarding specific targets for LDL-C and high-density lipoprotein cholesterol (HDL-C), blood pressure, body mass index (BMI), physical activity, and other appropriate lifestyle modifications (44). These health care teams can be hospital-, office-, or community-based and may include

chronic disease management or cardiac rehabilitation/secondary prevention programs. The family should be instructed on how best to further support the patient by encouraging reasonable changes in risk behavior (e.g., cooking AHA, Mediterranean, or DASH [Dietary Approach to Stop Hypertension] diet meals for the entire family; exercising together). This is particularly important when screening of family members reveals common risk factors, such as dyslipidemia, hypertension, second-hand smoke, and obesity. Of recent concern is the national trend to obesity, which has increased over the past decade in all 50 states, and its risk consequences (636). The combination of evidence-based therapies provides complementary, added morbidity and mortality reductions (637,638); prescription of and compliance with these combination therapies should be stressed.

5.2.1. Antiplatelet Therapy

See Figure 11 for antiplatelet therapy recommendations in algorithm format.

CLASS I

1. For UA/NSTEMI patients treated medically without stenting, aspirin* (75 to 162 mg per day) should be prescribed indefinitely *(Level of Evidence: A)*; clopidogrel† (75 mg per day) should be prescribed for at least 1 month *(Level of Evidence: A)* and ideally for up to 1 year. *(Level of Evidence: B)*
2. For UA/NSTEMI patients treated with bare-metal stents, aspirin* 162 to 325 mg per day should be prescribed for at least 1 month *(Level of Evidence: B)*, then continued indefinitely at a dose of 75 to 162 mg per day *(Level of Evidence: A)*; clopidogrel should be prescribed at a dose of 75 mg per day for a minimum of 1 month and ideally for up to 1 year (unless the patient is at increased risk of bleeding; then it should be given for a minimum of 2 weeks). *(Level of Evidence: B)*
3. For UA/NSTEMI patients treated with DES, aspirin* 162 to 325 mg per day should be prescribed for at least 3 months after sirolimus-eluting stent implantation and 6 months after paclitaxel-eluting stent implantation then continued indefinitely at a dose of 75 to 162 mg per day. *(Level of Evidence: B)* Clopidogrel 75 mg daily should be given for at least 12 months to all post-PCI patients receiving DES. *(Level of Evidence: B)*
4. Clopidogrel 75 mg daily (preferred) or ticlopidine (in the absence of contraindications) should be given to patients recovering from UA/NSTEMI when ASA is contraindicated or not tolerated because of hypersensitivity or gastrointestinal intolerance (but with gastroprotective agents such as proton-pump inhibitors). *(Level of Evidence: A)*

CLASS IIa

For UA/NSTEMI patients in whom the physician is concerned about the risk of bleeding, a lower initial aspirin dose after PCI of 75 to 162 mg per day is reasonable. *(Level of Evidence: C)*

CLASS IIb

For UA/NSTEMI patients who have an indication for anticoagulation, add warfarin‡ to maintain an international normalization ratio of 2.0 to 3.0.§ *(Level of Evidence: B)*

CLASS III

Dipyridamole is not recommended as an antiplatelet agent in post-UA/NSTEMI patients because it has not been shown to be effective. *(Level of Evidence: A)*

5.2.2. Beta Blockers

CLASS I

1. Beta blockers are indicated for all patients recovering from UA/NSTEMI unless contraindicated. (For those at low risk, see Class IIa recommendation below). Treatment should begin within a few days of the event, if not initiated acutely, and should be continued indefinitely. *(Level of Evidence: B)*
2. Patients recovering from UA/NSTEMI with moderate or severe LV failure should receive beta-blocker therapy with a gradual titration scheme. *(Level of Evidence: B)*

CLASS IIa

It is reasonable to prescribe beta blockers to low-risk patients (i.e., normal LV function, revascularized, no high-risk features) recovering from UA/NSTEMI in the absence of absolute contraindications. *(Level of Evidence: B)*

5.2.3. Inhibition of the Renin-Angiotensin-Aldosterone System

CLASS I

1. Angiotensin-converting enzyme inhibitors should be given and continued indefinitely for patients recovering from UA/NSTEMI with HF, LV dysfunction (LVEF less than 0.40), hypertension, or diabetes mellitus, unless contraindicated. *(Level of Evidence: A)*
2. An angiotensin receptor blocker should be prescribed at discharge to those UA/NSTEMI patients who are intolerant of an ACE inhibitor and who have either clinical or radiological signs of HF and LVEF less than 0.40. *(Level of Evidence: A)*
3. Long-term aldosterone receptor blockade should be prescribed for UA/NSTEMI patients without significant renal dysfunction (estimated creatinine clearance should be greater than 30 mL per min) or hyperkalemia (potassium should be less than or equal to 5 mEq per liter) who are already receiving therapeutic doses of an ACE inhibitor, have an LVEF less than or equal to 0.40, and have either symptomatic HF or diabetes mellitus. *(Level of Evidence: A)*

CLASS IIa

1. Angiotensin-converting enzyme inhibitors are reasonable for patients recovering from UA/NSTEMI in the absence of LV dysfunction, hypertension, or diabetes mellitus unless contraindicated. *(Level of Evidence: A)*

*For ASA-allergic patients, use clopidogrel alone (indefinitely), or try aspirin desensitization.
†For clopidogrel-allergic patients, use ticlopidine 250 mg by mouth twice daily.

‡Continue ASA indefinitely and warfarin longer term as indicated for specific conditions such as atrial fibrillation; LV thrombus; or cerebral, venous, or pulmonary emboli.
§An INR of 2.0 to 2.5 is preferable while given with ASA and clopidogrel, especially in older patients and those with other risk factors for bleeding.

2. Angiotensin-converting enzyme inhibitors are reasonable for patients with HF and LVEF greater than 0.40. *(Level of Evidence: A)*
3. In UA/NSTEMI patients who do not tolerate ACE inhibitors, an angiotensin receptor blocker can be useful as an alternative to ACE inhibitors in long-term management provided there are either clinical or radiological signs of HF and LVEF less than 0.40. *(Level of Evidence: B)*

CLASS IIb

The combination of an ACE inhibitor and an angiotensin receptor blocker may be considered in the long-term management of patients recovering from UA/NSTEMI with persistent symptomatic HF and LVEF less than 0.40* despite conventional therapy including an ACE inhibitor or an angiotensin receptor blocker alone. *(Level of Evidence: B)*

Data on the utility of ACE inhibitors in stable CAD in the presence of HF and LV dysfunction have been compelling, whereas data in their absence have been conflicting. A reduction in the rates of mortality and vascular events was reported in the Heart Outcomes Prevention Evaluation (HOPE) Study (343) with the long-term use of an ACE inhibitor (ramipril) in moderate-risk patients with CAD, many of whom had preserved LV function, as well as patients at high risk of developing CAD. Similar but smaller benefits were reported in the EUROPA study (EUropean trial on Reduction Of cardiac events with Perindopril in patients with stable coronary Artery disease), which observed a significant reduction in incidence of cardiovascular death, MI, or cardiac arrest among moderate-risk patients with known coronary disease without apparent HF randomized to perindopril versus placebo (639). Conflicting results, however, were observed in the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial, which found no significant difference in the risk of cardiovascular death, MI, or coronary revascularization among low-risk patients with stable CAD and preserved LV function when an ACE inhibitor (trandolapril) was added to modern conventional therapy (640); however, a subsequent meta-analysis of these 3 major trials supported benefit across the risk spectrum studied (641). These and other data may be harmonized by postulating that ACE inhibitors provide general benefit in stable CAD but that the absolute benefit is proportional to disease-related risk, with those at lowest risk benefiting least (641,642). These and other agents that may be used in patients with chronic CAD are listed in Table 22 and are discussed in detail in the ACC/AHA Guidelines for the Management of Patients With Chronic Stable Angina (4).

5.2.4. Nitroglycerin

CLASS I

1. Nitroglycerin to treat ischemic symptoms is recommended. *(Level of Evidence: C)*

5.2.5. Calcium Channel Blockers

CLASS I

1. Calcium channel blockers† are recommended for ischemic symptoms when beta blockers are not successful. *(Level of Evidence: B)*
2. Calcium channel blockers† are recommended for ischemic symptoms when beta blockers are contraindicated or cause unacceptable side effects. *(Level of Evidence: C)*

5.2.6. Warfarin Therapy

CLASS I

Use of warfarin in conjunction with ASA and/or clopidogrel is associated with an increased risk of bleeding and should be monitored closely. *(Level of Evidence: A)*

CLASS IIb

Warfarin either without (INR 2.5 to 3.5) or with low-dose ASA (75 to 81 mg per d; INR 2.0 to 2.5) may be reasonable for patients at high CAD risk and low bleeding risk who do not require or are intolerant of clopidogrel. *(Level of Evidence: B)*

5.2.7. Lipid Management

CLASS I

1. The following lipid recommendations are beneficial:
   a. Lipid management should include assessment of a fasting lipid profile for all patients, within 24 h of hospitalization. *(Level of Evidence: C)*
   b. Hydroxymethyl glutaryl-coenzyme A reductase inhibitors (statins), in the absence of contraindications, regardless of baseline LDL-C and diet modification, should be given to post-UA/NSTEMI patients, including postrevascularization patients. *(Level of Evidence: A)*
   c. For hospitalized patients, lipid-lowering medications should be initiated before discharge. *(Level of Evidence: A)*
   d. For UA/NSTEMI patients with elevated LDL-C (greater than or equal to 100 mg per dL), cholesterol-lowering therapy should be initiated or intensified to achieve an LDL-C of less than 100 mg per dL. *(Level of Evidence: A)* Further titration to less than 70 mg per dL is reasonable. (Class IIa, *Level of Evidence: A)*
   e. Therapeutic options to reduce non–HDL-C‡ are recommended, including more intense LDL-C–lowering therapy. *(Level of Evidence: B)*
   f. Dietary therapy for all patients should include reduced intake of saturated fats (to less than 7% of total calories), cholesterol (to less than 200 mg per d), and trans fat (to less than 1% of energy). *(Level of Evidence: B)*
   g. Promoting daily physical activity and weight management are recommended. *(Level of Evidence: B)*
2. Treatment of triglycerides and non-HDL-C is useful, including the following:
   a. If triglycerides are 200 to 499 mg per dL, non-HDL-C‡ should be less than 130 mg per dL. *(Level of Evidence: B)*

*The safety of this combination has not been proven in patients also on aldosterone antagonist and is not recommended.

†Short-acting dihydropyridine calcium channel antagonists should be avoided.
‡Non-HDL-C = total cholesterol minus HDL-C.

Table 22. Medications Used for Stabilized UA/NSTEMI Patients

Anti-Ischemic and Antithrombotic/Antiplatelet Agents	Drug Action	Class/Level of Evidence
Aspirin	Antiplatelet	I/A
Clopidogrel* or ticlopidine	Antiplatelet when aspirin is contraindicated	I/A
Beta blockers	Anti-ischemic	I/B
ACEI	EF less than 0.40 or HF EF greater than 0.40	I/A IIa/A
Nitrates	Antianginal	I/C for ischemic symptoms
Calcium channel blockers (short-acting dihydropyridine antagonists should be avoided)	Antianginal	I for ischemic symptoms; when beta blockers are not successful (B) or contraindicated, or cause unacceptable side effects (C)
Dipyridamole	Antiplatelet	III/A
Agents for Secondary Prevention and Other Indications	**Risk Factor**	**Class/Level of Evidence**
HMG-CoA reductase inhibitors	LDL cholesterol greater than 70 mg per dL	Ia
Fibrates	HDL cholesterol less than 40 mg per dL	IIa/B
Niacin	HDL cholesterol less than 40 mg per dL	IIa/B
Niacin or fibrate	Triglycerides 200 mg per dL	IIa/B
Antidepressant	Treatment of depression	IIb/B
Treatment of hypertension	Blood pressure greater than 140/90 mm Hg or greater than 130/80 mm Hg if kidney disease or diabetes present	I/A
Hormone therapy (initiation)†	Postmenopausal state	III/A
Treatment of diabetes	HbA_{1C} greater than 7%	I/B
Hormone therapy (continuation)†	Postmenopausal state	III/B
COX-2 inhibitor or NSAID	Chronic pain	IIa/C, IIb/C or III/C
Vitamins C, E, beta-carotene; folic acid, B6, B12	Antioxidant effect; homocysteine lowering	III/A

*Preferred to ticlopidine.†For risk reduction of coronary artery disease.
ACEI = angiotensin-converting enzyme inhibitor; CHF = congestive heart failure; COX-2 = cyclooxygenase 2; EF = ejection fraction; HDL = high-density lipoprotein; HMG-CoA = hydroxymethyl glutaryl coenzyme A; INR = international normalized ratio; LDL = low-density lipoprotein; NSAID = nonsteroidal anti-inflammatory drug; NSTEMI = non–ST-segment elevation myocardial infarction; UA = unstable angina.

b. If triglycerides are greater than or equal to 500 mg per dL*, therapeutic options to prevent pancreatitis are fibrate† or niacin† before LDL-lowering therapy is recommended. It is also recommended that LDL-C be treated to goal after triglyceride-lowering therapy. Achievement of a non-HDL-C‡ less than 130 mg per dL (i.e., 30 mg per dL greater than LDL-C target) if possible is recommended. *(Level of Evidence: C)*

CLASS IIa

1. The following lipid management strategies can be beneficial:
   a. Further reduction of LDL-C to less than 70 mg per dL is reasonable. *(Level of Evidence: A)*
   b. If baseline LDL cholesterol is 70 to 100 mg per dL, it is reasonable to treat LDL-C to less than 70 mg per dL. *(Level of Evidence: B)*
   c. Further reduction of non-HDL-C‡ to less than 100 mg per dL is reasonable; if triglycerides are 200 to 499 mg per dL, non-HDL-C target is less than 130 mg per dL. *(Level of Evidence: B)*
   d. Therapeutic options to reduce non-HDL-C‡ (after LDL-C lowering) include niacin† or fibrate* therapy.
   e. Nicotinic acid (niacin)† and fibric acid derivatives (fenofibrate, gemfibrozil)* can be useful as therapeutic options (after LDL-C–lowering therapy) for HDL-C less than 40 mg per dL. *(Level of Evidence: B)*
   f. Nicotinic acid (niacin)† and fibric acid derivatives (fenofibrate, gemfibrozil)* can be useful as therapeutic options (after LDL-C–lowering therapy) for triglycerides greater than 200 mg per dL. *(Level of Evidence: B)*
   g. The addition of plant stanol/sterols (2 g per d) and/or viscous fiber (more than 10 g per d) is reasonable to further lower LDL-C. *(Level of Evidence: A)*

CLASS IIb

Encouraging consumption of omega-3 fatty acids in the form of fish§ or in capsule form (1 g per d) for risk reduction may be reasonable. For treatment of elevated triglycerides, higher doses (2 to 4 g per d) may be used for risk reduction. *(Level of Evidence: B)*

There is a wealth of evidence that cholesterol-lowering therapy for patients with CAD and hypercholesterolemia (643) or with mild cholesterol elevation (mean 209 to 218 mg per dL) after MI and UA reduces vascular events and death (644,645). Moreover, recent trials have provided

*Patients with very high triglycerides should not consume alcohol. The use of bile acid sequestrants is relatively contraindicated when triglycerides are greater than 200 mg per dL.
†The combination of high-dose statin plus fibrate can increase risk for severe myopathy. Statin doses should be kept relatively low with this combination. Dietary supplement niacin must not be used as a substitute for prescription niacin.
‡Non-HDL-C = total cholesterol minus HDL-C.

§Pregnant and lactating women should limit their intake of fish to minimize exposure to methylmercury.

mounting evidence that statin therapy is beneficial regardless of whether the baseline LDL-C level is elevated (646–648). More aggressive therapy has resulted in suppression or reversal of coronary atherosclerosis progression and lower cardiovascular event rates, although the impact on total mortality remains to be clearly established (649). These data are discussed more fully elsewhere (3,17,39).

For patients with CHD or CHD equivalents (i.e., atherosclerosis in other vascular territories, diabetes mellitus, or 10-year estimated cardiovascular risk greater than 20%), the NCEP Adult Treatment Panel III recommended a target LDL-C level less than 100 mg per dL (17). Therapeutic lifestyle changes are recommended as well. Therapeutic lifestyle changes include diet, weight management, and increased physical activity. Specific diet recommendations include restriction of calories from saturated fat to less than 7% of total caloric intake and of cholesterol to less than 200 mg per d. Additionally, increased soluble fiber (10 to 25 g per d) and plant stanols/sterols (2 g per d) are noted as therapeutic lifestyle change dietary options to enhance LDL-C lowering. Reduction in trans fat (to less than 1% of caloric intake) subsequently has been added to prevention guidelines (3,38). These guidelines also recommend consideration of drug therapy if LDL-C is above goal range, either simultaneously with therapeutic lifestyle changes or sequentially, after 3 months of therapeutic lifestyle changes.

An update to the Adult Treatment Panel III guidelines was published in mid 2004 (16). The major change recommended in this update is an LDL-C treatment goal of less than 70 mg per dL as a reasonable option in very-high-risk patients (such as after UA/NSTEMI). Furthermore, if a high-risk patient has high triglycerides (greater than 200 mg per dL) or low HDL-C (less than 40 mg per dL), consideration can be given to combining a fibrate or nicotinic acid with an LDL-lowering drug. For moderately high-risk patients (2 or more risk factors and 10-year risk of 10% to 20%), the recommended LDL-C goal is less than 130 mg per dL, but an LDL-C goal of less than 100 mg per dL is a reasonable option. When drug therapy is utilized in moderate- to high-risk patients, it is advised that the intensity of the treatment be sufficient to achieve a reduction in LDL-C levels of at least 30% to 40%. Therapeutic lifestyle changes to modify existing lifestyle-based risk factors are strongly urged regardless of LDL-C levels.

Two trials further support early intensive lipid lowering after ACS. In the PROVE-IT TIMI 22 study (PRavastatin Or atorVastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22), 4,162 patients within 10 d of ACS were randomized to 40 mg of pravastatin or 80 mg of atorvastatin daily (648). The median LDL-C achieved in the moderately intensive (standard-dose) pravastatin group was 95 mg per dL compared with a median of 62 mg per dL in the aggressive, high-dose atorvastatin group. A 16% reduction in the HR for the primary composite end point of all-cause death, MI, UA requiring rehospitalization, revascularization (performed at least 30 d after randomization), and stroke was observed in favor of the high-dose regimen. The second trial, phase Z of the A to Z Trial (647), compared early initiation of an intensive statin regimen (simvastatin 40 mg per d for 1 month followed by 80 mg per d thereafter) with a delayed initiation of a less-intensive regimen (placebo for 4 months followed by simvastatin 20 mg per d) in patients with ACS. No difference was observed between the groups during the first 4 months of follow-up for the primary end point (composite of cardiovascular death, nonfatal MI, readmission for ACS, and stroke). However, from 4 months through the end of the study, the primary end point was significantly reduced in the aggressive treatment arm, which represented a favorable trend toward a reduction of major cardiovascular events with the early, aggressive statin regimen. The incidence of myopathy (CK greater than 10 times the upper limit of normal, with muscle symptoms) occurred more frequently in the early/aggressive treatment group, which reinforces the need for careful monitoring and follow-up with aggressive treatment.

Observational studies have generally supported initiation of lipid-lowering therapy before discharge after ACS both for safety and for early efficacy (event reduction) (650). In contrast, a meta-analysis of randomized trials of early (less than 14 d) initiation of lipid lowering after ACS, although supporting its safety, suggests that efficacy is generally delayed beyond 4 months (651).

Short- and long-term compliance is a clear benefit of in-hospital initiation of lipid lowering (652). In a demonstration project, the Cardiovascular Hospitalization Atherosclerosis Management Program, the in-hospital initiation of lipid-lowering therapy increased the percentage of patients treated with statins 1 year later from 10% to 91%, and for those with an LDL-C less than 100 mg per dL, the percentage increased from 6% to 58% (653), which suggests that predischarge initiation of lipid-lowering therapy enhances long-term compliance. Thus, there appear to be no adverse effects and substantial advantages to the initiation of lipid-lowering therapy before hospital discharge (652,654). Such early initiation of therapy also has been recommended in the update of the third report of the NCEP (16). Adherence to statin therapy was shown to be associated with improved survival in a large, population-based longitudinal observational study (655).

5.2.8. Blood Pressure Control

CLASS I

Blood pressure control according to JNC 7 guidelines* is recommended (i.e., blood pressure less than 140/90 mm Hg or less than 130/80 mm Hg if the patient has diabetes mellitus or chronic kidney disease). *(Level of Evidence: A)* Additional measures recommended to treat and control blood pressure include the following:

*Chobanian AV, Bakris GL, Black HR, et al., for the National High Blood Pressure Education Program Coordinating Committee. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560–72 (656).

a. Patients should initiate and/or maintain lifestyle modifications, including weight control, increased physical activity, alcohol moderation, sodium reduction, and emphasis on increased consumption of fresh fruits, vegetables, and low-fat dairy products. *(Level of Evidence: B)*

b. For patients with blood pressure greater than or equal to 140/90 mm Hg (or greater than or equal to 130/80 mm Hg for individuals with chronic kidney disease or diabetes mellitus), it is useful to add blood pressure medication as tolerated, treating initially with beta blockers and/or ACE inhibitors, with addition of other drugs such as thiazides as needed to achieve target blood pressure. *(Level of Evidence: A)*

All patients with elevated systolic or diastolic blood pressures should be educated and motivated to achieve targeted hypertensive control according to JNC 7 guidelines (656) adapted to patients with ischemic heart disease (656a). Systolic and diastolic blood pressures should be in the normal range (i.e., less than 140/90 mm Hg; 130/80 mm Hg if the patient has diabetes mellitus or chronic kidney disease).

5.2.9. Diabetes Mellitus

CLASS I

Diabetes management should include lifestyle and pharmacotherapy measures to achieve a near-normal HbA1c level of less than 7%. *(Level of Evidence: B)* Diabetes management should also include the following:

a. Vigorous modification of other risk factors (e.g., physical activity, weight management, blood pressure control, and cholesterol management) as recommended should be initiated and maintained. *(Level of Evidence: B)*

b. It is useful to coordinate the patient's diabetic care with the patient's primary care physician or endocrinologist. *(Level of Evidence: C)*

Glycemic control during and after ACS is discussed in Section 6.2.1.

Overweight patients should be instructed in a weight loss regimen, with emphasis on the importance of regular exercise and a lifelong prudent diet to maintain ideal body mass index. Patients should be informed and encouraged that even small reductions in weight can have positive benefits. This can be reassuring to severely obese patients. In the Diabetes Prevention Program study, 3,234 overweight subjects with elevated fasting and postload plasma glucose concentrations were randomized to treatment with metformin or a lifestyle modification program (657). The goals of the lifestyle modification program were targeted to at least a 7% weight loss and at least 150 min of physical activity per week. The incidence of diabetes mellitus was reduced by 58% in the lifestyle modification group and 31% in the metformin group compared with placebo. The study supports the substantial positive effects of even modest changes in weight and physical activity on the development of diabetes, a major risk factor for cardiovascular events (657–659).

5.2.10. Smoking Cessation

CLASS I

Smoking cessation and avoidance of exposure to environmental tobacco smoke at work and home are recommended. Follow-up, referral to special programs, or pharmacotherapy (including nicotine replacement) is useful, as is adopting a stepwise strategy aimed at smoking cessation (the 5 As are: Ask, Advise, Assess, Assist, and Arrange). *(Level of Evidence: B)*

For patients who smoke, persistent smoking cessation counseling is often successful and has substantial potential to improve survival. Daly et al. (660) quantified the long-term effects of smoking on patients with ACS. Men less than 60 years old who continued to smoke had a risk of death due to all causes that was 5.4 times that of men who stopped smoking (p less than 0.05). Referral to a smoking cessation program and the use of pharmacological agents including nicotine patches or gum are recommended (661).

Bupropion, an anxiolytic agent and weak inhibitor of neuronal uptake of neurotransmitters, has been effective when added to brief regular counseling sessions in helping patients to quit smoking. The treatment of 615 study subjects for 7 weeks resulted in smoking cessation rates of 28.8% for the 100 mg per d dosage and 44.2% for 300 mg per d compared with 19.6% for placebo-assigned patients (p less than 0.001) (661). The abstinence rate at 1 year was 23.0% for those treated with bupropion 300 mg per d versus 12.4% for those receiving placebo (661).

Recently, another nonnicotine replacement therapy, varenicline, was approved to assist in smoking cessation. Varenicline is a first-in-class nicotine acetylcholine receptor partial agonist, designed to provide some nicotine effects (easing withdrawal symptoms) and to block the effects of nicotine from cigarettes, discouraging smoking. Approval was based on demonstrated effectiveness in 6 clinical trials involving a total of 3,659 chronic cigarette smokers (32–34). In 2 of the 5 placebo-controlled trials, varenicline also was compared to buproprion and found to be more effective. Varenicline is given for an initial 12-week course. Successfully treated patients may continue treatment for an additional 12 weeks to improve the chances of long-term abstinence. Family members who live in the same household should also be encouraged to quit smoking to help reinforce the patient's effort and to decrease the risk of secondhand smoke for everyone.

5.2.11. Weight Management

CLASS I

Weight management, as measured by body mass index and/or waist circumference, should be assessed on each visit. A body mass index of 18.5 to 24.9 kg per m^2 and a waist circumference (measured horizontally at the iliac crest) of less than 40 inches for men and less than 35 inches for women is recommended. *(Level of Evidence: B)* Additional weight management practices recommended include the following:

a. On each patient visit, it is useful to consistently encourage weight maintenance/reduction through an appropriate balance of physical activity, caloric intake, and formal behavioral programs when indicated to maintain/achieve a body mass index between 18.5 and 24.9 kg per m^2. *(Level of Evidence: B)*

b. If waist circumference is 35 inches or more in women or 40 inches or more in men, it is beneficial to initiate lifestyle changes and consider treatment strategies for metabolic syndrome as indicated. *(Level of Evidence: B)*

c. The initial goal of weight loss therapy should be to reduce body weight by approximately 10% from baseline. With success, further weight loss can be attempted if indicated through further assessment. *(Level of Evidence: B)*

5.2.12. Physical Activity

CLASS I

1. The patient's risk after UA/NSTEMI should be assessed on the basis of an in-hospital determination of risk. A physical activity history or an exercise test to guide initial prescription is beneficial. *(Level of Evidence: B)*
2. Guided/modified by an individualized exercise prescription, patients recovering from UA/NSTEMI generally should be encouraged to achieve physical activity duration of 30 to 60 min per d, preferably 7 (but at least 5) d per week of moderate aerobic activity, such as brisk walking, supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, gardening, and household work). *(Level of Evidence: B)*
3. Cardiac rehabilitation/secondary prevention programs are recommended for patients with UA/NSTEMI, particularly those with multiple modifiable risk factors and/or those moderate- to high-risk patients in whom supervised exercise training is particularly warranted. *(Level of Evidence: B)*

CLASS IIb

The expansion of physical activity to include resistance training on 2 d per week may be reasonable. *(Level of Evidence: C)*

Federal and ACC/AHA guidelines recommend that all Americans strive for at least 30 to 60 min of moderate physical activity most days of the week, preferably daily (662). The 30 to 60 min can be spread out over 2 or 3 segments during the day. For post-UA/NSTEMI patients, daily walking can be encouraged immediately after discharge. Excellent resource publications on exercise prescription in cardiovascular patients are available (45,663). Physical activity is important in efforts to lose weight because it increases energy expenditure and plays an integral role in weight maintenance. Regular physical activity reduces symptoms in patients with CVD, improves functional capacity, and improves other cardiovascular risk factors such as insulin resistance and glucose intolerance (45). Beyond the instructions for daily exercise, patients require specific instruction on those strenuous activities (e.g., heavy lifting, climbing stairs, yard work, and household activities) that are permissible and those they should avoid. Several activity questionnaires or nomograms, specific to the cardiac population and general population, have been developed to help guide the patient's exercise prescription if an exercise test is not available (664–667). As emphasized by the US Public Health Service, comprehensive cardiac rehabilitation services include long-term programs involving medical evaluation, prescribed exercise, cardiac risk factor modification, education, and counseling (668). These programs are designed to limit the physiological and psychological effects of cardiac illness, reduce the risk for sudden death or reinfarction, control cardiac symptoms, and enhance the psychosocial and vocational status of selected patients. Enrollment in a cardiac rehabilitation program after discharge can enhance patient education and compliance with the medical regimen and assist with the implementation of a regular exercise program (45,47,573,669,670). In addition to aerobic training, mild- to moderate-resistance training may be considered. This can be started 2 to 4 weeks after aerobic training has begun (671). Expanded physical activity is an important treatment component for the metabolic syndrome, which is becoming increasingly prevalent.

Exercise training can generally begin within 1 to 2 weeks after UA/NSTEMI treated with PCI or CABG to relieve ischemia (663). Unsupervised exercise may target a heart rate range of 60% to 75% of maximum predicted; supervised training (see Section 5.4) may target a somewhat higher heart rate (70% to 85% of maximum predicted) (663). Additional restrictions apply when residual ischemia is present.

5.2.13. Patient Education

CLASS I

Beyond the detailed instructions for daily exercise, patients should be given specific instruction on activities (e.g., heavy lifting, climbing stairs, yard work, and household activities) that are permissible and those that should be avoided. Specific mention should be made regarding resumption of driving, return to work, and sexual activity. *(Level of Evidence: C)* Specific recommendations for physical activity follow in Section 5.4.

Patients should be educated and motivated to achieve appropriate target LDL-C and HDL-C goals. Patients who have undergone PCI or CABG derive benefit from cholesterol lowering (672) and deserve special counseling lest they mistakenly believe that revascularization obviates the need for significant lifestyle changes. The NHLBI "Your Guide to Better Health" series provides useful educational tools for patients (http://hp2010.nhlbihin.net/yourguide/).

5.2.14. Influenza

CLASS I

An annual influenza vaccination is recommended for patients with cardiovascular disease. *(Level of Evidence: B)*

5.2.15. Depression

CLASS IIa

It is reasonable to consider screening UA/NSTEMI patients for depression and refer/treat when indicated. *(Level of Evidence: B)*

5.2.16. Nonsteroidal Anti-Inflammatory Drugs

CLASS I

At the time of preparation for hospital discharge, the patient's need for treatment of chronic musculoskeletal discomfort should be assessed, and a stepped-care approach to treatment should be used for selection of treatments (Fig. 21). Pain relief should begin with acetaminophen, small doses of narcotics, or nonacetylated salicylates. *(Level of Evidence: C)*

CLASS IIa

It is reasonable to use nonselective NSAIDs, such as naproxen, if initial therapy with acetaminophen, small doses of narcotics, or nonacetylated salicylates is insufficient. *(Level of Evidence: C)*

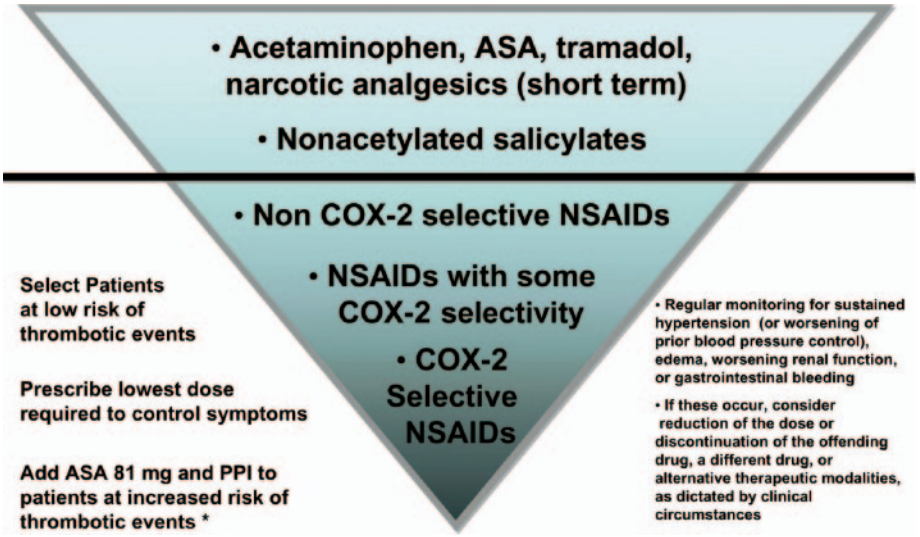

Figure 21. Stepped-Care Approach to Pharmacological Therapy for Musculoskeletal Symptoms With Known Cardiovascular Disease or Risk Factors for Ischemic Heart Disease

*Addition of ASA may not be sufficient protection against thrombotic events. Reproduced with permission. American Heart Association Scientific Statement on the Use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDS)-An Update for Clinicians © 2007, American Heart Association, Inc. (673). ASA = aspirin; COX-2 = cyclooxygenase-1; NSAIDs = nonsteroidal anti-inflammatory drugs; PPI = proton-pump inhibitor.

CLASS IIb

Nonsteroidal anti-inflammatory drugs with increasing degrees of relative COX-2 selectivity may be considered for pain relief only for situations in which intolerable discomfort persists despite attempts at stepped-care therapy with acetaminophen, small doses of narcotics, nonacetylated salicylates, or nonselective NSAIDs. In all cases, the lowest effective doses should be used for the shortest possible time. ***(Level of Evidence: C)***

CLASS III

Nonsteroidal anti-inflammatory drugs with increasing degrees of relative COX-2 selectivity should not be administered to UA/NSTEMI patients with chronic musculoskeletal discomfort when therapy with acetaminophen, small doses of narcotics, nonacetylated salicylates, or nonselective NSAIDs provides acceptable levels of pain relief. ***(Level of Evidence: C)***

The selective COX-2 inhibitors and other nonselective NSAIDs have been associated with increased cardiovascular risk. The risk appears to be amplified in patients with established CVD (1,359–362). In a large Danish observational study of first-time MI patients (n = 58,432), the HRs and 95% CIs for death were 2.80 (2.41 to 3.25) for rofecoxib, 2.57 (2.15 to 3.08) for celecoxib, 1.50 (1.36 to 1.67) for ibuprofen, 2.40 (2.09 to 2.80) for diclofenac, and 1.29 (1.16 to 1.43) for other NSAIDS (361). There were dose-related increases in risk of death and non–dose-dependent trends for rehospitalization for MI for all drugs (360,361). An AHA scientific statement on the use of NSAIDS concluded that the risk of cardiovascular events is proportional to COX-2 selectivity and the underlying risk in the patient (673). Nonpharmacological approaches were recommended as the first line of treatment, followed by the stepped-care approach to pharmacological therapy, as shown in Figure 21.

5.2.17. Hormone Therapy

CLASS III

1. **Hormone therapy with estrogen plus progestin, or estrogen alone, should not be given de novo to postmenopausal women after UA/NSTEMI for secondary prevention of coronary events.** ***(Level of Evidence: A)***
2. **Postmenopausal women who are already taking estrogen plus progestin, or estrogen alone, at the time of UA/NSTEMI in general should not continue hormone therapy. However, women who are more than 1 to 2 years past the initiation of hormone therapy who wish to continue such therapy for another compelling indication should weigh the risks and benefits, recognizing the greater risk of cardiovascular events and breast cancer (combination therapy) or stroke (estrogen). Hormone therapy should not be continued while patients are on bedrest in the hospital.** ***(Level of Evidence: B)***

Although prior observational data suggested a protective effect of hormone therapy for coronary events, a randomized trial of hormone therapy for secondary prevention of death and MI (Heart and Estrogen/progestin Replacement Study [HERS]) failed to demonstrate a beneficial effect (674). Disturbingly, there was an excess risk for death and MI early after hormone therapy initiation. The Women's Health Initiative included randomized primary prevention trials of estrogen plus progestin and estrogen alone. Both trials were stopped early owing to an observed increased risk related to hormone therapy that was believed to outweigh the potential benefits of further study (675–677). It is recommended that postmenopausal women receiving hormone therapy at

the time of a cardiovascular event discontinue its use. Likewise, hormone therapy should not be initiated for secondary prevention of coronary events. However, there may be other permissible indications for hormone therapy in postmenopausal women (e.g., prevention of perimenopausal symptoms such as flushing, or prevention of osteoporosis) if the benefits are believed to outweigh the increased cardiovascular risk).

5.2.18. Antioxidant Vitamins and Folic Acid

CLASS III

1. Antioxidant vitamin supplements (e.g., vitamins E, C, or beta carotene) should not be used for secondary prevention in UA/NSTEMI patients. *(Level of Evidence: A)*
2. Folic acid, with or without B6 and B12, should not be used for secondary prevention in UA/NSTEMI patients. *(Level of Evidence: A)*

Although there is an association of elevated homocysteine blood levels and CAD, a reduction in homocysteine levels with routine folate supplementation was not demonstrated to reduce the risk of CAD events in 2 trials (Norwegian Vitamin Trial [NORVIT] and HOPE) that included post-MI or high risk, stable patients (678–681). Similarly, a large clinical trials experience with antioxidant vitamins has failed to demonstrate benefit for primary or secondary prevention (38,681a).

5.3. Postdischarge Follow-Up

RECOMMENDATIONS

CLASS I

1. Detailed discharge instructions for post-UA/NSTEMI patients should include education on medications, diet, exercise, and smoking cessation counseling (if appropriate), referral to a cardiac rehabilitation/secondary prevention program (when appropriate), and the scheduling of a timely follow-up appointment. Low-risk medically treated patients and revascularized patients should return in 2 to 6 weeks, and higher risk patients should return within 14 d. *(Level of Evidence: C)*
2. Patients with UA/NSTEMI managed initially with a conservative strategy who experience recurrent signs or symptoms of UA or severe (Canadian Cardiovascular Society class III) chronic stable angina despite medical management who are suitable for revascularization should undergo timely coronary angiography. *(Level of Evidence: B)*
3. Patients with UA/NSTEMI who have tolerable stable angina or no anginal symptoms at follow-up visits should be managed with long-term medical therapy for stable CAD. *(Level of Evidence: B)*
4. Care should be taken to establish effective communication between the post-UA/NSTEMI patient and health care team members to enhance long-term compliance with prescribed therapies and recommended lifestyle changes. *(Level of Evidence: B)*

The risk of death within 1 year can be predicted on the basis of clinical information and the ECG (see also Section 3.3). In a study of 515 survivors of hospitalization for NSTEMI, risk factors included persistent ST-segment depression, HF, advanced age, and ST-segment elevation at discharge (682). Patients with all high-risk markers present had a 14-fold greater mortality rate than did patients with all markers absent. Elevated cardiac TnT levels have also been demonstrated to provide independent prognostic information for cardiac events at 1 to 2 years. For patients with ACS in a GUSTO-IIa substudy, age, ST-segment elevation on admission, prior CABG, TnT, renal insufficiency, and severe chronic obstructive pulmonary disease were independently associated with risk of death at 1 year (683,684). For UA/NSTEMI patients, prior MI, TnT positivity, accelerated angina before admission, and recurrent pain or ECG changes were independently associated with risk of death at 2 years. Patients managed with an initial conservative strategy (see Section 3) should be reassessed at the time of return visits for the need for cardiac catheterization and revascularization. Specifically, the presence and severity of angina should be ascertained. Rates of revascularization during the first year have been reported to be high (685). Long-term (7 years) follow-up of 282 patients with UA demonstrated high event rates during the first year (MI 11%, death 6%, PTCA 30%, and CABG 27%); however, after the first year, event rates were low (685). Independent risk factors for death/MI were age greater than 70 years, diabetes, and male sex. A predictive model for the risk of death from discharge to 6 months after an ACS has been developed and validated using the 17,142-patient GRACE registry database (168). Mortality averaged 4.8%. Nine predictive variables were identified: older age, history of MI, history of HF, increased pulse rate at presentation, lower systolic blood pressure at presentation, elevated initial serum creatinine level, elevated initial serum cardiac biomarker levels, ST-segment depression on presenting ECG, and not having a PCI performed in the hospital. The C statistic for the validation cohort was 0.75. The GRACE tool was suggested to be a simple, robust tool for clinical use.

Certain patients at high risk of ventricular tachyarrhythmia after UA/NSTEMI may be candidates for an implantable cardioverter defibrillator. Indications and timing of an implantable cardioverter defibrillator in this setting are presented in the STEMI guidelines (1) and more recently the Ventricular Arrhythmias and Sudden Cardiac Death guidelines (686). Indications for testing for atherosclerotic disease in other vascular beds (i.e., carotid, peripheral arterial) are also covered elsewhere in recent guidelines (687).

Major depression has also been reported to be an independent risk factor for cardiac events after MI and occurs in up to 25% of such patients (688). Antidepressant therapy (with sertraline) was safe and effective for relief of depressive symptoms in a controlled trial in 369 depressed patients with ACS, but it did not conclusively demonstrate a beneficial effect on cardiovascular end points, perhaps because of limited sample size (689). Cognitive therapy and, in some cases, sertraline did not affect late survival after MI in another randomized study (Enhancing Recovery in Coronary Heart Disease [ENRICHD]), but those whose depression did not improve were at higher risk of late mortality

(690). The CREATE trial evaluated interpersonal psychotherapy (IPT) compared with clinical management and the selective serotonin reuptake inhibitor citalopram compared with placebo in a 2 × 2 factorial design among patients with CAD and major depression (691). The primary end point of Hamilton Depression Rating Scale score was improved in the citalopram group versus placebo (mean reduction 14.9 vs. 11.6, $p = 0.005$) but did not differ for IPT versus clinical management (mean reduction 12.1 vs. 14.4, $p = 0.06$). Likewise, the secondary end point of reduction in mean Beck Depression Inventory score was improved in the citalopram group but did not differ for IPT.

Patients recognized to be at high risk for a cardiac event after discharge for any of the above reasons should be seen for follow-up earlier and more frequently than lower-risk patients.

The overall long-term risk for death or MI 2 months after an episode of UA/NSTEMI is similar to that of other CAD patients with similar characteristics. Van Domburg et al. (685) reported a good long-term outcome even after a complicated early course. Based on a median follow-up of almost 8 years, mortality in the first year was 6%, then 2% to 3% annually in the following years (685). When the patient has returned to the baseline level, typically 6 to 8 weeks after hospitalization, arrangements should be made for long-term regular follow-up visits, as for stable CAD. Cardiac catheterization with coronary angiography is recommended for any of the following situations: 1) significant increase in anginal symptoms, including recurrent UA; 2) high-risk pattern (e.g., at least 2 mm of ST-segment depression, systolic blood pressure decline of at least 10 mm Hg) on exercise test (see Section 3.4); 3) HF; 4) angina with mild exertion (inability to complete stage 2 of the Bruce protocol for angina); and 5) survivors of sudden cardiac death. Revascularization is recommended based on the coronary anatomy and ventricular function (see Section 4, ACC/AHA Guidelines for the Management of Patients With Chronic Stable Angina [4], and ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery [555]).

Minimizing the risk of recurrent cardiovascular events requires optimizing patients' compliance with prescribed therapies and recommended lifestyle modifications. Many studies exploring predictors of compliance have failed to find predictive value in simple demographic or socioeconomic variables. More reliable predictors are the patients' beliefs and perceptions about their vulnerability to disease and the efficacy of the prescribed treatments and, importantly, various aspects of the relationship with their health care provider (692–694). Development of a therapeutic relationship with the patient and family is likely to enhance compliance. Care should be taken to ensure that there is adequate time spent with the family focused on explanation of the disease and proposed treatments, the importance of adhering to the prescribed treatment plan, and exploration of patient-specific barriers to compliance. Participation in cardiac rehabilitation/secondary prevention programs can help reinforce patient-specific secondary prevention issues and can address barriers to compliance. Close communication between the treating physician and the cardiac rehabilitation team is important to maximize effectiveness (3,47,695,696).

5.4. Cardiac Rehabilitation

CLASS I

Cardiac rehabilitation/secondary prevention programs, when available, are recommended for patients with UA/NSTEMI, particularly those with multiple modifiable risk factors and those moderate- to high-risk patients in whom supervised or monitored exercise training is warranted. ***(Level of Evidence: B)***

Cardiac rehabilitation programs are designed to limit the physiological and psychological effects of cardiac illness, reduce the risk for sudden death or reinfarction, control cardiac symptoms, stabilize or reverse the atherosclerotic process, and enhance the psychosocial and vocational status of selected patients (668,695,697). Cardiac rehabilitation is a comprehensive long-term program that involves medical evaluation, prescribed exercise, cardiac risk factor modification, education, and counseling (668,698). Cardiac rehabilitation may occur in a variety of settings, including medically supervised groups in a hospital, physician's office, or community facility (696). Exercise may involve a stationary bicycle, treadmill, calisthenics, walking, or jogging, and monitoring may include ECG telemetry, depending on a patient's risk status and the intensity of exercise training. Education and counseling concerning risk factor modification are individualized, and close communication between the treating physician and cardiac rehabilitation team may promote long-term behavioral change (695,696). Alternative delivery approaches, including home exercise, internet-based, and transtelephonic monitoring/supervision, can be implemented effectively and safely for carefully selected clinically stable patients (668,699).

Witt et al. (700) examined the association of participation in cardiac rehabilitation with survival in Olmstead County, Minnesota, and found that participants had a lower risk of death and recurrent MI at 3 years (p less than 0.001 and $p = 0.049$, respectively). The survival benefit associated with participation was stronger in more recent years (700). In this study, half of the eligible patients participated in cardiac rehabilitation after MI, although women and older adult patients were less likely to participate, independent of other characteristics.

A pooled-effect estimate for total mortality for the exercise-only intervention demonstrated a reduction in all-cause mortality (random effects model OR 0.73 [95% CI 0.54 to 0.98]) compared with usual care. Comprehensive cardiac rehabilitation reduced all-cause mortality, although to a lesser degree (OR 0.87 [95% CI 0.71 to 1.05]). Neither of the interventions had an effect on the occurrence of nonfatal MI. The authors concluded that exercise-based cardiac rehabilitation appeared to be effective in reducing

cardiac deaths but that it was still unclear whether an exercise-only or a comprehensive cardiac rehabilitation intervention was more beneficial. The population studied was predominantly male, middle-aged, and low risk. The authors suggested that those who could have benefited from the intervention might have been excluded owing to age, gender, or comorbidity. The authors cautioned that the results were of limited reliability because the quality of reporting in the studies was generally poor, and there were high losses to follow-up (698).

Cardiac rehabilitation comprising exercise training and education, counseling, and behavioral interventions yielded improvements in exercise tolerance with no significant cardiovascular complications, improvements in symptoms (decreased anginal pain and improved symptoms of HF such as shortness of breath and fatigue), and improvements in blood lipid levels; reduced cigarette smoking in conjunction with a smoking cessation program; decreased stress; and improved psychosocial well-being (668). In addition to reductions in total cholesterol and LDL-C, increases in HDL-C levels occur (701).

Cardiac rehabilitation has been reported to improve prognosis after MI in a cost-effective manner (702,703). In current practice, referrals for cardiac rehabilitation are more frequent after bypass surgery and less frequent after PCI for UA/NSTEMI (704). Benefits of rehabilitation after uncomplicated UA/NSTEMI with revascularization and modern medical therapy are less clear in comparison with STEMI or complicated NSTEMI.

Existing community studies reveal that fewer than one third of patients with MI receive information or counseling about cardiac rehabilitation before being discharged from the hospital (668,705). Only 16% of patients in a study of 5 hospitals in 2 Michigan communities were referred to a cardiac rehabilitation program at discharge, and only 26% of the patients later interviewed in the community reported actual participation in such a program; however, 54% of the patients referred at discharge did participate at the time of their follow-up interview (705). Physician referral was the most powerful predictor of patient participation in a cardiac rehabilitation program. In a longitudinal study of the use of inpatient cardiac rehabilitation in 5,204 Worcester, Mass, residents hospitalized with MI in seven 1-year periods between 1986 and 1997, patients not referred to inpatient cardiac rehabilitation were less likely to be prescribed effective cardiac medications and to undergo risk factor modification counseling before discharge (706).

Patient reasons for nonparticipation and noncompliance include affordability of service, insurance coverage/noncoverage, social support from a spouse or other caregiver, gender-specific attitudes, patient-specific internal factors such as anxiety or poor motivation, and logistical and financial constraints, or a combination of these factors (688,705). Women and the elderly are referred less frequently to cardiac rehabilitation programs, even though they derive benefit from them (38,707–710). Health care systems should consider instituting processes that encourage referral of appropriate patients to cardiac rehabilitation/secondary prevention programs (for example, the use of standardized order sets that facilitate this, such as the AHA "Get with the Guidelines" tools). In addition, it is important that referring health care practitioners and cardiac rehabilitation teams communicate in ways that promote patient participation. Of note, Medicare coverage for rehabilitation recently was expanded beyond post-MI, post-CABG, and stable angina to include PCI (711).

5.5. Return to Work and Disability

Return-to-work rates after MI, which currently range from 63% (712) to 94% (713), are difficult to influence because they are confounded by factors such as job satisfaction, financial stability, and company policies (714). In PAMI (Primary Angioplasty in Myocardial Infarction)-II, a study of primary PTCA in low-risk patients with MI (i.e., age less than 70 years, ejection fraction greater than 0.45, 1- or 2-vessel disease, and good PTCA result), patients were encouraged to return to work at 2 weeks (715). The actual timing of return to work was not reported, but no adverse events occurred as a result of this strategy.

Cardiac rehabilitation programs after MI can contribute to reductions of mortality and improved physical and emotional well-being (see Section 5.4). Patients whose expectations for return to work were addressed in rehabilitation returned to work at a significantly faster rate than the control group in a prospective study (716).

Lower or absent levels of depressive symptoms before MI increases the odds of recovery of functional status (717). Patients with high pre-event functional independence measurement have a shorter length of stay and a greater likelihood of discharge to home (718). Pre-event peak aerobic capacity and depression score are the best independent predictors of postevent physical function. Women tend to have lower physical function scores than men of similar age, depression score, and comorbidity. Resting LVEF is not a predictor of physical function score.

Patients' cardiac functional states are not a strong predictor of their probability of returning to work. Diabetes, older age, Q-wave MI, and preinfarction angina are associated with failure to resume full employment (719). However, psychological variables such as trust, job security, patient feelings about disability, expectations of recovery by both physician and patient, and degree of somatizing are more predictive (720,721). Physical requirements of the job play a role as well (719,721).

To aid occupational physicians in making return-to-work decisions, Froom et al. (719) studied the incidence of post- MI events at 1, 2, 4, 6, 9, and 12 months. Events included cardiac death, recurrent infarction, CHF, and UA. They found that the incidence of events reached a low steady state at 10 weeks.

Return to work can be determined by employer regulations rather than by the patient's medical condition. It behooves the physician to provide data to prove that the patient's job does

Table 23. Energy Levels Required to Perform Some Common Activities

Less Than 3 METS	3–5 METS	5–7 METS	7–9 METS	More Than 9 METS
		Self-Care		
Washing	Cleaning windows	Easy digging in garden	Sawing wood	Carrying loads upstairs (objects more than 90 lb)
Shaving	Raking	Level hand lawn mowing	Heavy shoveling	
Dressing	Power lawn mowing	Climbing stairs (slowly)	Climbing stairs (moderate speed)	Climbing stairs (quickly)
Desk work	Bed making/stripping	Carrying objects (30 to 60 lb)	Carrying objects (60 to 90 lb)	
Washing dishes	Carrying objects (15 to 30 lb)		Digging vigorously	Shoveling heavy snow
Driving auto				
Light housekeeping				
		Occupational		
Sitting (clerical/ assembly)	Stocking shelves (light objects)	Carpentry (exterior)	Digging ditches (pick and shovel)	Lumber jack
Typing	Auto repair	Shoveling dirt	Forestry	Heavy laborer
Desk work	Light welding/carpentry	Sawing wood	Farming	Shoveling (heavy)
Standing (store clerk)		Operating pneumatic tools		
		Recreational		
Golf (cart)	Dancing (social)	Badminton (competitive)	Canoeing	Handball
Knitting	Golf (walking)	Tennis (singles)	Mountain climbing	Football (competitive)
Hand sewing	Sailing	Snow skiing (downhill)	Paddle ball	Squash
	Tennis (doubles)	Light backpacking	Walking (5 mph)	Ski touring
	Volleyball (6 persons)	Basketball	Running (12 min. mile)	Vigorous basketball (game)
	Table tennis	Football	Mountain or rock climbing	
	Marital sex	Stream Fishing	Soccer	
		Physical Conditioning		
Walking (2 mph)	Level walking (3–4 mph)	Level walking (4.5–5.0 mph)	Level jogging (5 mph)	Running (more than 6 mph)
Stationary bike	Level biking (6–8 mph)	Bicycling (9–10 mph)	Swimming (crawl stroke)	
Very light calisthenics	Light calisthenics	Swimming, breast stroke	Rowing machine	Bicycling (more than 13 mph)
			Heavy calisthenics	Rope jumping
			Bicycling (12 mph)	Walking uphill (5 mph)

Adapted with permission from Haskell WL. Design and implementation of cardiac conditioning program. In: Wenger NL, Hellerstein HK, editors. Rehabilitation of the Coronary Patient. New York, NY: Churchill Livingstone, 1978 (725).

METS = metabolic equivalents; mph = miles per hour.

not impose a prohibitive risk for a cardiac event. An example is the case of Canadian bus drivers reported by Kavanagh et al. (722). These patients were evaluated with a stress test. The physician and technologist studied the drivers at work and showed that the cardiac stress values during driving were only half of the average values obtained in the stress laboratory. The calculated risk of sudden cardiovascular incidents causing injury or death to passengers, other road users, and the drivers themselves in the first year after recovery from an MI was 1 in 50,000 driving-years. The bus drivers were allowed to return to work after they satisfied the Canadian Cardiovascular Society guidelines.

Covinsky et al. (723) performed a mail survey study of patients with MIs. Three months after discharge, women reported worse physical and mental health and were more likely to work less than before the MI. Similarly, women were less likely to return to work than men. Contemporary information specific to UA/NSTEMI on return to work by gender is needed.

The current aggressive interventional treatment of ACS will have an impact on mortality, morbidity, and hospital length of stay (724). It remains to be determined whether earlier improvement in cardiac condition after ACS will have an effect on the rate of return to work because of the multiple noncardiac factors that influence disability and return to work.

5.6. Other Activities

In patients who desire to return to physically demanding activities early, the safety of the activity can be determined by comparing performance on a graded exercise test with the MET level required for the desired activity. Table 23 presents energy levels, expressed in METS, required to perform a variety of common activities (725). This and similar tables can be helpful in translating a patient's performance on a graded exercise test into daily activities that can be undertaken with reasonable safety.

The health care provider should provide explicit advice about when to return to previous levels of physical activity, sexual activity, and employment. Daily walking can be encouraged immediately (726). In stable patients without complications (Class I), sexual activity with the usual partner can be resumed within 1 week to 10 d. Driving can begin 1 week after discharge if the patient is judged to be in compliance with individual state laws. Each state's Department of Motor Vehicles or its equivalent has mandated certain criteria, which vary from state to state and must be met before operation of a motor vehicle after serious illness

(727). These include such caveats as the need to be accompanied and to avoid stressful circumstances such as rush hour, inclement weather, night driving, heavy traffic, and high speeds. For patients who have experienced a complicated MI (one that required CPR or was accompanied by hypotension, serious arrhythmias, high-degree block, or CHF), driving should be delayed 2 to 3 weeks after symptoms have resolved.

Most commercial aircraft are pressurized to 7,500 to 8,000 feet and therefore could cause hypoxia due to the reduced alveolar oxygen tension. The maximum level of pressurization is limited to 8,000 feet (2440 m) by Federal Aviation Administration regulation (728). Therefore, air travel within the first 2 weeks of MI should be undertaken only if there is no angina, dyspnea, or hypoxemia at rest or fear of flying. The individual must have a companion, must carry NTG, and must request airport transportation to avoid rushing and increased cardiac demands. Availability of an emergency medical kit and automated external defibrillator has been mandated as of April 12, 2004 (729), in all aircraft that carry at least approximately 30 passengers and have at least 1 flight attendant.

Patients with UA (i.e., without infarction) who are revascularized and otherwise stable may accelerate return to work, driving, flying, and other normal activities (often, within a few days).

5.7. Patient Records and Other Information Systems

Effective medical record systems that document the course and plan of care should be established or enhanced. Both paper-based and electronic systems that incorporate evidence-based guidelines of care, tools for developing customized patient care plans and educational materials, and capture of data for appropriate standardized quality measurements should be implemented and used routinely. Examples of such tools are the ACC's "Guidelines Applied in Practice" and the AHA's "Get With the Guidelines." All computerized provider order entry (CPOE) systems should incorporate these attributes as well. In some settings, the regular and consistent use of such systems and tools has been shown to significantly improve quality of care and patient safety. The patient's medical record from the time of hospital discharge should indicate the discharge medical regimen, the major instructions about postdischarge activities and rehabilitation, and the patient's understanding and plan for adherence to the recommendations. After resolution of the acute phase of UA/NSTEMI, the medical record should summarize cardiac events, current symptoms, and medication changes since hospital discharge or the last outpatient visit and should document the plan for future care. Processes for effective and timely transfer of relevant prehospital and postdischarge patient information between all participating caregivers should be continuously enhanced in accordance with existing regulatory standards. This should include providing all patients with the tools to facilitate access to and understanding of the nature and importance of their most current plan of care. With the increasing numbers of patients who have regular access to the Internet, awareness of online information reflecting current evidence-based and professionally developed standards of care should be encouraged and promoted. Several sites with reliable health care information relevant to UA/NSTEMI are available to patients (http://www.heartauthority.com; http://www.nhlbi.nih.gov/health/dci/index.html; http://www.nlm.nih.gov/medlineplus/tutorial.html; and http://www.fda.gov/hearthealth/index.html).

6. Special Groups

6.1. Women

RECOMMENDATIONS

CLASS I

1. **Women with UA/NSTEMI should be managed with the same pharmacological therapy as men both in the hospital and for secondary prevention, with attention to antiplatelet and anticoagulant doses based on weight and renal function; doses of renally cleared medications should be based on estimated creatinine clearance.** ***(Level of Evidence: B)***
2. **Recommended indications for noninvasive testing in women with UA/NSTEMI are similar to those for men.** ***(Level of Evidence: B)***
3. **For women with high-risk features, recommendations for invasive strategy are similar to those of men. See Section 3.3.** ***(Level of Evidence: B)***
4. **In women with low-risk features, a conservative strategy is recommended.** ***(Level of Evidence: B)***

Although at any age, women have a lower incidence of CAD than men, they account for a considerable proportion of UA/NSTEMI patients, and UA/NSTEMI is a serious and common condition among women. It is important to overcome long-held notions that severe coronary manifestations are uncommon in this population; however, women can manifest CAD somewhat differently than men (679). Women who present with chest discomfort are more likely than men to have noncardiac causes and cardiac causes other than fixed obstructive coronary artery stenosis. Other cardiac causes include coronary vasospasm, abnormal vasodilator reserve, and other mechanisms (679,731–733). Women with CAD are, on average, older than men and are more likely to have comorbidities such as hypertension, diabetes mellitus, and HF with preserved systolic function; to manifest angina rather than MI; and, among angina and MI patients, to have atypical symptoms (150,734–736).

6.1.1. Profile of UA/NSTEMI in Women

Considerable clinical information about UA/NSTEMI in women has emerged from many randomized trials and registries (150,552,554,734,737). As in other forms of CAD, women are older and have more comorbidities (diabetes mellitus and hypertension) and stronger family

histories than men (150,734–736). Women are less likely to have had a previous MI or cardiac procedures (734), more likely to have a history of HF, but less likely to have LV systolic dysfunction. Women present with symptoms of similar frequency, duration, and pattern, but more often than men, they have anginal-equivalent symptoms such as dyspnea or atypical symptoms (72,141,738). The frequency of ST-segment changes is similar to that for men, but women more often have T-wave inversion. There are notable differences in the profiles of cardiac biomarkers for women and men, with a consistent finding in trials and registries that women less often have elevated levels of troponin (552,554,565,737). In an analysis of TACTICS-TIMI 18, women also less often had elevation of CK-MB; however, women more often had increased levels of high-sensitivity CRP or BNP than men. Importantly, the prognostic value of elevated biomarkers is similar in men and women (739). Coronary angiograms in both trials and registries revealed less extensive CAD in women, as well as a higher proportion with nonobstructive CAD. The rate of nonobstructive CAD can be as high as 37% despite selection of women according to strict inclusion criteria in clinical trials (150,554).

A differing symptom pattern in women than men, the lower frequency of positive cardiac biomarkers despite high rates of ST-T abnormalities on the ECG, and the higher frequency of nonobstructive CAD in women make it challenging to confirm the diagnosis of UA/NSTEMI. This is a likely cause of underutilization of several therapies in women compared with men (737). There are important mechanisms of ischemic chest pain other than platelet/thrombus aggregates on plaque erosion or ulceration in women (see Section 6.8). Although some studies report that female sex is a risk factor for poor outcome in UA/NSTEMI on the basis of unadjusted event rates, (72,737), multivariate models have not found female sex to be an independent risk factor for death, reinfarction, or recurrent ischemia. This is in contrast to an apparent independent risk of death for women compared with men with STEMI, particularly for younger women.

6.1.2. Management

6.1.2.1. PHARMACOLOGICAL THERAPY

In studies that span the spectrum of CAD, women tend to receive less intensive pharmacological treatment than men (734,737,740), perhaps in part because of a general perception of lower frequency and severity of CAD in women. Although the specifics vary regarding beta blockers and other drugs (150,734,741), a consistent (and disturbing) pattern is that women are prescribed ASA and other antithrombotic agents less frequently than men (150,737,740). Women derive the same treatment benefit as men from ASA, clopidogrel (54), anticoagulants, beta blockers, ACE inhibitors, and statins (54,742). A meta-analysis of GP IIb/IIIa antagonists in ACS demonstrated an interaction between sex and treatment effect, with an apparent lack of efficacy in women (526); however, women with elevated troponin levels received the same beneficial effect as men treated with GP IIb/IIIa antagonists. The findings of a beneficial effect of a direct invasive strategy in women treated with a GP IIb/IIIa antagonist in TACTICS-TIMI 18 (see Section 6.1.2.3) further supports the similar efficacy of these agents in this cohort of women and men.

Despite the clear benefit of antiplatelet and anticoagulant therapy for women with ACS, women are at increased risk of bleeding. A low maintenance dose of ASA (75 to 162 mg) should be used to reduce the excess bleeding risk, especially in combination with clopidogrel (54). Estimated creatinine clearance instead of serum creatinine levels should guide decisions about dosing and the use of agents that are renally cleared, e.g., LMWHs and the small-molecule GP IIb/IIIa antagonists. In a large community-based registry study, 42% of patients with UA/NSTEMI received excessive initial dosing of at least 1 antiplatelet or anticoagulant agent (UFH, LMWH, or GP IIb/IIIa inhibitor) (743). Female sex, older age, renal insufficiency, low body weight, and diabetes were predictors of excessive dosing. Dosing errors predicted an increased risk of major bleeding (743). The formula used to estimate creatinine clearance for dose adjustment in clinical studies and labeling that defines adjustments for several medications have been based on the Cockroft-Gault formula for estimating creatinine clearance, which is not identical to the Modification of Diet and Renal Disease (MDRD) formula recently recommended for screening for renal disease (744), either in units or cutpoints for adjustment. Weight-based adjustment of medication doses also should be applied carefully where recommended.

The use of hormone therapy in postmenopausal women is discussed in Section 5.2.17.

6.1.2.2. CORONARY ARTERY REVASCULARIZATION

Contemporary studies have cast doubt on the widely held belief that women fare worse with PCI and CABG than do men because of technical factors (e.g., smaller artery size, greater age, and more comorbidities) (150,735,742,745–749). In the case of PCI, it has been suggested that angiographic success and late outcomes are similar in women and men, although in some series, early complications occurred more frequently in women (745,746,750–753). However, the outlook for women undergoing PCI appears to have improved, as evidenced by the NHLBI PTCA registry (754). Earlier studies of women undergoing CABG showed that women were less likely to receive internal mammary arteries or complete revascularization and had a higher mortality rate (RR 1.4 to 4.4) than men (748,749,755). However, more recent studies of CABG in patients with ACS show a more favorable outlook for women than previously thought (see Section 6.3) (756,757,757a).

A Mayo Clinic review of 3,014 patients (941 women) with UA who underwent PCI reported that women had

similar early and late results as men (735). The BARI trial of 1,829 patients compared PTCA and CABG, primarily in patients with UA, and showed that the results of revascularization were, if anything, better in women than men when corrected for other factors. At an average 5.4-year follow-up, mortality rates for men and women were 12% and 13%, respectively, but when adjusted for baseline differences (e.g., age, diabetes, and other comorbidities), there was a lower risk of death (RR 0.60, 95% CI 0.43 to 0.84, $p = 0.003$) but a similar risk of death or MI (RR 0.84, 95% CI 0.66 to 1.07, $p = 0.16$) in women compared with men (755). The NHLBI Dynamic Registry has reported improved outcomes for women who underwent PCI in 1997 to 1998 compared with 1985 to 1986. Compared with men, women had similar procedural success, in-hospital death, MI, and CABG (754). Although the 1-year event rate was higher for women, female sex was not independently associated with death or MI because women tended to be older and had more comorbidities. A prospective study of 1,450 patients with UA/NSTEMI who underwent an indirect or direct invasive strategy with coronary stenting reported that female sex was independently associated with a lower rate of death and MI (HR 0.51, 95% CI 0.28 to 0.95) (553).

6.1.2.3. INITIAL INVASIVE VERSUS INITIAL CONSERVATIVE STRATEGY

In the modern era, clinical trials assessing a direct invasive strategy compared with an initial conservative strategy for the management of UA/NSTEMI have consistently demonstrated a benefit for men (552,554,565). Approximately one third of the cohorts in these trials were women (n = 2,179), and the results on the efficacy and safety of a direct invasive strategy in women have been conflicting. Each trial was underpowered to evaluate the subgroup of women, and there were substantial differences among the trials (Table 24). A meta-analysis of trials in the era of stents and GP IIb/IIIa antagonists has failed to show a survival benefit of a direct invasive strategy in women at 6 to 12 months (OR for women 1.07, 95% CI 0.82 to 1.41; OR for men 0.68, 95% CI 0.57 to 0.81) (542).

In TACTICS-TIMI 18, there was a significant reduction in the primary end point of death, nonfatal MI, or rehospitalization for an ACS with a direct invasive strategy (OR 0.45, 95% CI 0.24 to 0.88, $p = 0.02$) (182). All subjects in this trial (n = 754) were treated with an early GP IIb/IIIa antagonist (tirofiban). A similar overall reduction in the primary composite end point of death, MI, or rehospitalization for ACS at 6 months was observed for women and men (adjusted OR 0.72, 95% CI 0.47 to 1.11 and adjusted OR 0.64, 95% CI 0.47 to 0.88, respectively). Women were older, more frequently had hypertension, and less frequently had previous MI, CABG, and elevated cardiac biomarkers (p less than 0.001 for all), but there was no significant difference in TIMI risk score distribution by sex ($p = 0.76$) (565). A similar reduction in composite risk was observed in women with intermediate (3 to 4) or high (5 to 7) TIMI risk scores as in men. However, in contrast to men with a low TIMI risk score who had similar outcomes with an invasive and conservative strategy, low-risk women had an OR for events of 1.59 (95% CI 0.69 to 3.67) for the invasive compared with the conservative strategy (565). However, the number of events was small (n = 26 events), and the p value for interaction between strategy, TIMI risk score, and sex on outcome did not achieve significance ($p = 0.09$). An elevated biomarker, including BNP, CRP, CK-MB, and troponin, also identified women (and men) who benefited differentially from a direct invasive strategy. The reduction in risk was enhanced in women with elevated TnT levels (adjusted OR 0.47, 95% CI 0.26 to 0.83), with a similar reduction in the primary end point noted for women and men with elevated troponin. However, in contrast to the similar outcome for the invasive versus conservative strategy in men with a negative TnT marker (OR 1.02, 95% CI 0.64 to 1.62, $p = 0.04$), the primary end point of death, MI, and rehospitalization occurred significantly more frequently in women with negative troponin randomized to an invasive strategy (OR 1.46, 95% CI 0.78 to 2.72) (565).

The RITA-3 trial enrolled 682 women (38% of 1,810 patients) (758). There was a significant interaction between sex and treatment strategy (invasive versus conservative) on outcome in RITA-3 ($p = 0.042$). In contrast to a reduction in death or MI for men assigned to an invasive strategy, the HR for women was 1.09. Women assigned to an initial conservative strategy had a lower rate of death and MI (5.1%) at 1 year than the women enrolled in TACTICS-TIMI 18 (9.7% at 6 months). Consistent with this difference, 37% of women in RITA-3 had no significant obstructive CAD, compared with 17% of women in TACTICS-TIMI 18 (759). Other notable differences between RITA-3 and TACTICS-TIMI 18 include routine use of GP IIb/IIIa antagonist in TACTICS-TIMI 18 and different criteria for the MI end point in both the conservative and the invasive treatment groups. The RITA-3 investigators have reported that the rates of death and MI for women are 11.1% and 12.7% in the conservative versus invasive strategy, respectively, that is, not significantly different, when there was a lower threshold for cardiac marker diagnosis of MI among the conservatively treated group (554).

In the only trial that showed an overall survival benefit for an invasive strategy, FRISC-II, there was a significant interaction in outcome between treatment strategy, which included a systematic but delayed interventional approach within 7 d of symptom onset, and sex (549,552). Thirty percent of the 2,457 enrolled patients were women, and the death and MI rate at 1 year was nonsignificantly higher for invasively treated versus conservatively treated women, in contrast to a large reduction in death and MI for men. Female sex was independently associated with events in the invasively assigned patients. However, the poor outcome of women was largely driven by a 9.9% death rate at 1 year in women who underwent CABG. In contrast, the death rate for women who underwent PCI in the invasive strategy

Table 24. Invasive Versus Conservative Strategy Results for UA/NSTEMI by Gender

Study (Reference)	Timing	End Point	Overall Result	Results in Men	Results in Women	Comment
TACTICS-TIMI 18 (182,565) 2002 n = 2220 34% female	Angiography 4 to 48 h	Death, MI	30 d Inv: 4.7% Cons: 7.0%, $p = 0.02$ ARR = 2.3% 6 months Inv: 7.3% Cons: 9.5% OR = 0.74 (95% CI 0.54 to 1.00) ARR = 2.2%	6 months Inv: 7.6% Cons: 9.4% OR = 0.68 (95% CI 0.43 to 1.05) ARR = 1.8%	6 months Inv: 6.6% Cons: 9.7% OR = 0.45 (95% CI 0.24 to 0.88) ARR = 3.1%	Benefit greater in women with high cTnT; OR = 0.47 (95% CI 0.26 to 0.83) for death, MI, and rehospitalization
RITA-3 (758) 2002 n = 1810 38% female	Angiography within 48 h	Death, MI, refractory angina Death, MI	4 months Inv: 9.6% Cons: 14.5%, $p = 0.001$ RR = 0.66 (95% CI 0.51 to 0.85) ARR = 4.9% 1 year Inv: 7.0% Cons: 8.3%, $p = 0.58$ RR = 0.91 (95% CI 0.67 to 1.25) ARR = 0.7%	4 months Inv: 8.8% Cons: 17.3% ARR = 8.5% 1 year Inv: 7.0% Cons: 10.1% Arr = 3.1%	4 months Inv: 10.9% Cons: 9.6%, p = NS ARR = −1.3% 1 year Inv: 8.6% Cons: 5.1% ARR = −3.5%	Angina reduced with invasive strategy
FRISC II (245,549,552) 1999 n = 2457 30% female	Revascularization within 7 d	Death, MI	6 months Inv: 9.4% Cons: 12.1%, $p = 0.3$ ARR = 2.7% 1 year Inv: 10.4% Cons: 14.1%, $p = 0.005$ ARR = 3.7%	1 year Inv: 9.6% Cons: 15.8% p less than 0.001 ARR = 6.2%	6 months Inv: 10.5% Cons: 8.3%, RR = 1.26 (95% CI 0.80 to 1.97) ARR = −1.9% 1 year Inv: 12.4% Cons: 10.5%, p = NS ARR = −1.9%	Mortality benefit at 1 year (2.2% vs. 3.9%) ARR = 1.7% $p = 0.02$, not seen in women (4% vs. 3.3%) ARR = −0.7%
TIMI-IIIB (150) 1997 n = 1423 34% female	Angiography 1 to 48 h	Death, MI	1 year Inv: 10.8% Cons: 12.2%, $p = 0.42$ ARR = 1.4%	Death at 6 weeks Inv: 2.6% Cons: 1.4% ARR = −1.2% MI at 6 weeks Inv: 5.5% Cons: 6.0% ARR = 0.5%	Death at 6 weeks Inv: 2% Cons: 4.4% ARR = 2.4% MI at 6 weeks Inv: 4.4% Cons: 5.2% ARR = 0.8%	Invasively treated patients had less angina and fewer rehospitalizations for ischemia

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ACS = acute coronary syndrome; ARR = absolute risk reduction; CI = confidence interval; Cons = conservative; cTnT = cardiac troponin T; FRISC II = Fast Revascularization during InStability in Coronary artery disease-II; Inv = invasive; MI = myocardial infarction; n = number of patients; NS = nonsignificant; NSTEMI = non–ST-segment elevation MI; OR = odds ratio; PTCA = percutaneous transluminal coronary angioplasty; RITA-3 = Third Randomized Intervention Treatment of Angina; RR = risk ratio; TACTICS-TIMI 18 = Treat Angina with Aggrastat and determine Cost of Therapy with Invasive or Conservative Strategy–Thrombolysis In Myocardial Infarction 18; TIMI IIIB = Thrombolysis In Myocardial Infarction III; UA = unstable angina.

group was similar to that of men (1.5% vs. 1.0%; RR 1.50, 95% CI 0.27 to 8.28; p = nonsignificant [NS]).

In summary, women with UA/NSTEMI and high-risk features, including elevated cardiac biomarkers, appear to benefit from an invasive strategy with early intervention and adjunctive GP IIb/IIIa antagonist use. There is no benefit of a direct invasive strategy for low-risk women, and the weight of evidence from the recent randomized clinical trials suggests that there may be excess risk associated with a direct invasive strategy in this group. The challenges in the diagnosis of UA/NSTEMI and the varied pathophysiology of ischemic pain in women who present with rest discomfort suggest that perhaps the excess risk of a direct invasive strategy observed in low-risk women could be due to intervention on a stable incidental coronary lesion in a woman with another mechanism for rest pain.

6.1.3. Stress Testing

In general, ECG exercise testing is less predictive in women than in men, primarily because of the lower pretest probability of CAD (581,760–762). Perfusion studies using sestamibi have good sensitivity and specificity in women (763). Breast attenuation is less of a problem than previously with thallium-201 stress testing with new tissue software. Stress echocardiography (dobutamine or exercise) is therefore an accurate and cost-effective technique for CAD detection in women (581). Newer perfusion methods such as adenosine-stress CMR also appear to be promising in women. Cardiac magnetic resonance imaging (for function, perfusion, and viability) and multislice CCTA are 2 new diagnostic modalities that could prove particularly useful in women because of their promise of both greater sensitivity and specificity (improved diagnostic accuracy). Evidence of ischemia by objective measures without obstructive CAD carries an adverse prognosis (4,764) and is suggestive of vascular dysfunction (coronary endothelial or microvascular dysfunction) as an etiological mechanism.

Recommendations for noninvasive testing in women are the same as in men (see Section 3.4) (733,764). A report of 976 women who underwent treadmill exercise suggests that the Duke Treadmill Score provides accurate diagnostic and prognostic estimates in both women and men (765). The Duke Treadmill Score actually performed better for women than for men in the exclusion of CAD. There were fewer low-risk women than men with any significant CAD (at least 1 vessel with greater than 75% stenosis; 20% in women vs. 47% in men, p less than 0.001).

Regarding dobutamine stress echocardiography, pilot phase data from the Women's Ischemia Syndrome Evaluation (WISE) indicated that in women, the test reliably detects multivessel disease (sensitivity 81.8%, similar to that in men) but not 1-vessel disease (766). Several studies have indicated that women with positive stress tests tend not to be evaluated as aggressively as men (741), which is inappropriate given the adverse prognosis of ischemia as demonstrated in WISE and other studies (733,767–774).

In the TIMI IIIB registry, women underwent exercise testing in a similar proportion as men (150,734). The frequencies of stress test positivity were also similar, although women were less likely to have a high-risk stress test result. Moreover, women were less likely to undergo angiography (RR 0.71, p less than 0.001), perhaps because of the lower percentage with high-risk test results on noninvasive testing.

6.1.4. Conclusions

Women with UA/NSTEMI are older and more frequently have comorbidities compared with men but have more atypical presentations and appear to have less severe and less extensive obstructive CAD. Women receive ASA less frequently than do men, but patients with UA/NSTEMI of either sex benefit from and should receive this agent, as well as other Class I recommended agents. Doses should be adjusted on the basis of weight and estimated creatinine clearance for renally cleared drugs for all recommended agents when appropriate. Image-enhanced stress testing has similar prognostic value in women as in men.

6.2. Diabetes Mellitus

RECOMMENDATIONS

CLASS I

1. **Medical treatment in the acute phase of UA/NSTEMI and decisions on whether to perform stress testing, angiography, and revascularization should be similar in patients with and without diabetes mellitus. *(Level of Evidence: A)***
2. **In all patients with diabetes mellitus and UA/NSTEMI, attention should be directed toward aggressive glycemic management in accordance with current standards of diabetes care endorsed by the American Diabetes Association and the American College of Endocrinology. Goals of therapy should include a preprandial glucose target of less than 110 mg per dL and a maximum daily target of less than 180 mg per dL. The postdischarge goal of therapy should be HbA1C less than 7%, which should be addressed by primary care and cardiac caregivers at every visit. *(Level of Evidence: B)***
3. **An intravenous platelet GP IIb/IIIa inhibitor should be administered for patients with diabetes mellitus as recommended for all UA/NSTEMI patients (Section 3.2). *(Level of Evidence: A)* The benefit may be enhanced in patients with diabetes mellitus. *(Level of Evidence: B)***

CLASS IIa

1. **For patients with UA/NSTEMI and multivessel disease, CABG with use of the internal mammary arteries can be beneficial over PCI in patients being treated for diabetes mellitus. *(Level of Evidence: B)***
2. **Percutaneous coronary intervention is reasonable for UA/NSTEMI patients with diabetes mellitus with single-vessel disease and inducible ischemia. *(Level of Evidence: B)***
3. **In patients with UA/NSTEMI and diabetes mellitus, it is reasonable to administer aggressive insulin therapy to achieve a glucose less than 150 mg per dL during the first 3 hospital (intensive care unit) days and between 80 and 110 mg per dL thereafter whenever possible. *(Level of Evidence: B)***

Please see Section 4 for further explanation of revascularization strategies.

6.2.1. Profile and Initial Management of Diabetic and Hyperglycemic Patients With UA/NSTEMI

Coronary artery disease accounts for 75% of all deaths in patients with diabetes mellitus (50,51), and approximately 20% to 25% of all patients with UA/NSTEMI have diabetes (610,734,775–778). Patients with UA/NSTEMI and diabetes have more severe CAD (776,779,780), and diabetes is an important independent predictor for adverse outcomes (death, MI, or readmission with UA at 1 year; RR 4.9) (781–784). In addition, many patients with diabetes who present with UA/NSTEMI have already undergone CABG (785).

Patients with diabetes tend to have more extensive noncoronary vascular comorbidities, hypertension, LV hypertrophy, cardiomyopathy, and HF. In addition, autonomic dysfunction, which occurs in approximately one third of patients with diabetes, influences heart rate and blood pressure, raises the threshold for the perception of angina, and may be accompanied by LV dysfunction (786–788). On coronary angiography, patients with diabetes and UA have a greater proportion of ulcerated plaques (94% vs. 60%, $p = 0.01$) and intracoronary thrombi (94% vs. 55%, $p = 0.004$) than patients without diabetes (789). These findings suggest a higher risk of plaque instability.

According to American Diabetes Association standards of care (790), the relationship of controlled blood glucose levels and reduced mortality in the setting of MI has been demonstrated. The American College of Endocrinology has also emphasized the importance of careful control of blood glucose targets in the range of 110 mg per dL preprandially to a maximum of 180 mg per dL. In 1 study (791), admission blood glucose values were analyzed in consecutive patients with MI. Analysis revealed an independent association of admission blood glucose and mortality. The 1-year mortality rate was significantly lower in subjects with admission plasma glucose less than 101 mg per dL (5.6 mmol per liter) than in those with plasma glucose 200 mg per dL (11 mmol per liter). In the first Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study (792,793) insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with MI was examined. Mean blood glucose in the intensive insulin intervention arm was 172.8 mg per dL (9.5 mmol per liter) compared with 211 mg per dL (11.6 mmol per liter) in the "conventional" group. Overall, the intensive approach reduced long-term relative mortality (at 3.4 years of follow-up) by 25% in the insulin-treated group. The broad range of blood glucose levels within each arm limits the ability to define specific blood glucose target thresholds.

In the second DIGAMI study (794), 3 treatment strategies were compared in a randomized trial among 1,253 patients with type 2 diabetes mellitus and suspected MI: acute insulin-glucose infusion followed by insulin-based long-term glucose control, insulin-glucose infusion followed by standard glucose control, and routine metabolic management according to local practice. Blood glucose was reduced more at 24 h in those receiving insulin-glucose infusions, but long-term glucose control, assessed by HbA1C, did not differ between the groups, and the fasting glucose in group 1 (8.0 mmol per liter) did not reach target (5 to 7 mmol per liter). The primary end point of all-cause mortality between groups 1 and 2 did not differ significantly (23.4% vs. 22.6%) at a median of 2.1 years of follow-up. Morbidity also did not differ among the 3 groups. Although the DIGAMI-2 regimen of acutely introduced, long-term insulin treatment in the setting of suspected acute MI was not demonstrated to incrementally reduce morbidity and mortality, epidemiological analyses still support a strong, independent relationship between glucose levels and long-term mortality in patients with ischemic heart disease (794).

Attainment of targeted glucose control in the setting of cardiac surgery is associated with reduced mortality and risk of deep sternal wound infections in cardiac surgery patients with diabetes (795,796). This supports the concept that perioperative hyperglycemia is an independent predictor of infection in patients with diabetes mellitus, with the lowest mortality in patients with blood glucose less than or equal to 150 mg per dL (8.3 mmol per liter) (797).

A mixed group of patients with and without diabetes admitted to a surgical intensive care unit (ICU) were randomized to receive intensive insulin therapy (target blood glucose 80 to 110 mg per dL [4.4 to 6.1 mmol per liter]). Achievement of a mean blood glucose of 103 mg per dL (5.7 mmol per liter) reduced mortality during the ICU stay and decreased overall in-hospital mortality (798). Subsequent analysis demonstrated that for each 20-mg per dL (1.1-mmol per liter) glucose elevation above 100 mg per dL (5.5 mmol per liter), the risk of death during the ICU stay increased. Hospital and ICU survival were linearly associated with ICU glucose levels, with the highest survival rates occurring in patients achieving an average blood glucose less than or equal to 110 mg per dL (6.1 mmol per liter).

Although beta blockers can mask the symptoms of hypoglycemia or lead to it by blunting the hyperglycemic response, they nevertheless should be used with appropriate caution in patients with diabetes mellitus and UA/NSTEMI. Diuretics that cause hypokalemia can inhibit insulin release and thereby worsen glucose intolerance.

Elevated blood glucose among critically ill patients even in the absence of clinical diabetes mellitus has received recent attention as an important risk factor for mortality (799). A randomized trial in the surgical ICU setting (800) found that strict glycemic control with insulin reduced both morbidity and in-hospital mortality (800). More recently, the role of intensive insulin therapy in the medical ICU setting has been studied (801) in 1,200 medical ICU patients (some with CVD) randomized to conventional therapy (insulin administered when glucose exceeded 215 mg per dL, tapering infusion when glucose fell below 180 mg per dL) or to intensive insulin therapy (targeting a glucose of 80 to 110 mg per dL). Overall, intensive insulin

did not significantly reduce in-hospital mortality, the primary end point (37.3% in the intensive therapy arm, 40% in the conventional arm, $p = 0.33$), but secondary outcomes of acquired kidney injury, time to ventilator weaning, and ICU and hospital discharge stays were reduced. Hypoglycemia was more common but often consisted of a single, asymptomatic episode. However, when analysis was restricted to the intended population of 767 patients whose ICU stay was at least 3 d, in-hospital death was reduced from 52.5% to 43% ($p = 0.009$) and ICU death from 38.1% to 31.3% ($p = 0.005$). In addition, secondary outcomes of time to ventilator weaning, days to ICU discharge and to hospital discharge, acquired kidney injury, hyperbilirubinemia, and CRP levels were reduced. Pending results of additional randomized clinical trials (802), a reasonable approach is to apply a less aggressive glucose control strategy during the first 3 ICU days (e.g., goal of less than 150 mg per dL) in very ill patients (e.g., with ventilators or on parenteral feeding) (803). Thereafter, and in less ill patients, a more intensive insulin regimen could be instituted, with a goal of normoglycemia (80 to 110 mg per dL).

6.2.2. Coronary Revascularization

Approximately 20% of all patients who undergo CABG (804) and PCI (746,747,750,751,779,780) have diabetes mellitus. Data regarding outcomes are complex. In the Coronary Artery Surgery Study (CASS) of CABG, patients with diabetes had a 57% higher mortality rate than patients without diabetes. A striking advantage for CABG over PCI was found in treated patients with diabetes in the BARI trial (776), a randomized trial of PCI versus CABG in 1,829 stable patients with multivessel disease, of whom 19% were patients with diabetes (see Section 4). As in other studies, patients with diabetes mellitus had increased comorbidity rates. Five years after randomization, patients who required treatment for diabetes had a lower survival rate than patients without diabetes (73.1% vs. 91.3%, p less than 0.0001), whereas survival rates in patients without and with diabetes who did not require hypoglycemic treatment were similar (93.3% vs. 91.1%, p = NS). Outcomes for CABG in treated patients with diabetes were far better than those for PCI (80.6% vs. 65.5% survival, $p = 0.0003$). An interesting finding was that the mortality rate during the 5.4 years of the study in patients with diabetes who received SVGs (18.2%) was similar to that of patients who underwent PCI (20.6%); whereas the mortality rate in patients who received internal mammary arteries was much lower (2.9%). Results of the Emory Angioplasty versus Surgery Trial (EAST) at 8 years showed a similar trend but were less conclusive (805). The increased mortality rate noted in randomized trials in patients with diabetes treated with PTCA has been confirmed in a registry study from Emory University (613). Uncorrected, there was little difference in long-term mortality rates. The CABG patients had more severe disease, and with correction for baseline differences, there was an improved survival rate in insulin-requiring patients with multivessel disease who were revascularized with CABG rather than with PCI. That the more severely diseased patients, in a nonrandomized registry, were selectively sent more often for CABG than for PCI probably represents good clinical decision making.

A 9-year follow-up of the NHLBI registry showed a similar disturbing pattern for patients with diabetes undergoing PCI (779). Immediate angiographic success and completeness of revascularization were similar, but compared with patients without diabetes, patients with diabetes (who, again, had more severe CAD and comorbidities) had increased rates of hospital mortality (3.2% vs. 0.5%), nonfatal MI (7.0% vs. 4.1%), death and MI (10.0% vs. 4.5%), and the combined end point of death, MI, and CABG (11% vs. 6.7%; p less than 0.01 for all). At 9 years, rates of mortality (35.9% vs. 17.9%), MI (29% vs. 18.5%), repeat PCI (43.0% vs. 36.5%), and CABG (37.6% vs. 27.4%) were all higher in patients with diabetes than in those without (779).

However, as discussed in Section 4, other data point to a lesser differential effect of PCI in patients with diabetes. For example, data from the BARI registry varied from those of the BARI trial. In the registry, there was no significant difference in cardiac survival for patients with diabetes undergoing PCI (92.5%) and CABG (94%; p = NS) (615,806). In the Duke University registry, patients with diabetes and PCI or CABG were matched with the BARI population (807). The outcome in patients with diabetes was worse than that without diabetes with either CABG or PCI, but there was no differential effect by therapy. The 5-year survival rate for PCI and CABG adjusted for baseline characteristics was 86% and 89% in patients with diabetes and 92% and 93% without diabetes, respectively (807).

Stents could improve the outcome of patients with diabetes who undergo PCI. In a study with historical controls, the outcome after coronary stenting was superior to that after PTCA in patients with diabetes, and the restenosis rate after stenting was reduced (63% vs. 36%, diabetes vs. no diabetes with balloon PTCA at 6 months, $p = 0.0002$, compared with 25% and 27% with stents, p = NS) (805). On the other hand, patients with diabetes who underwent atherectomy had a substantial restenosis rate (60% over 6 months) (808). Using data derived from the Northern New England registries, a contemporary BARI-like comparison of long-term survival after PCI (64% with at least 1 stent) versus CABG found significantly better risk-adjusted long-term survival in CABG patients with 3-vessel disease (HR = 0.60, p less than 0.01) (809). Similar benefits of CABG over PCI were demonstrated for patients with diabetes.

Three trials have shown that abciximab considerably improved the outcome of PCI in patients with diabetes. In the EPILOG trial, abciximab resulted in a greater decline in death/MI over 6 months after PCI in patients with diabetes (HR 0.36, 95% CI 0.21 to 0.61) than in those without diabetes (HR 0.60, 95% CI 0.44 to 0.83) (810). Similar

results have been reported for tirofiban in the PRISM-PLUS trial (133,811). EPISTENT was a randomized trial that compared stent plus placebo with stent plus abciximab and balloon plus abciximab in 2,399 patients, of whom 20.5% had diabetes and 20.3% had UA (512). The 30-d event rate (death, MI, and urgent revascularization) in patients with diabetes declined from 12.1% (stent plus placebo) to 5.6% (stent plus abciximab; $p = 0.040$). At 6 months, the drug reduced revascularization of target arteries in patients with diabetes (16.6% vs. 8.1%, $p = 0.02$). Death or MI was reduced to a similar degree in patients with diabetes as that in patients without diabetes (812). These benefits were maintained at 1 year (813). Thus, in the 6-month data, initial GP IIb/IIIa therapy, as well as stenting, considerably improved the safety of PCI in patients with diabetes. In a comparative trial of abciximab and tirofiban (TARGET), both agents were associated with comparable event rates, including similar rates of 6-month target-vessel revascularization and 1-year mortality (814).

6.2.3. Conclusions

Diabetes occurs in approximately one fifth of patients with UA/NSTEMI and is an independent predictor of adverse outcomes. It is associated with more extensive CAD, unstable lesions, frequent comorbidities, and less favorable long-term outcomes with coronary revascularization, especially with PTCA. It is unclear whether these differences are due to more frequent restenosis and/or severe progression of the underlying disease (779). The use of stents, particularly with abciximab, appears to provide more favorable results in patients with diabetes, although more data are needed, including with DES. Coronary artery bypass grafting, especially with 1 or both internal mammary arteries, leads to more complete revascularization and a decreased need for reintervention than PCI, even when bare-metal stents are used in diabetic patients with multivessel disease. Given the diffuse nature of diabetic coronary disease, the relative benefits of CABG over PCI may well persist for diabetic patients, even in the era of DES.

6.3. Post-CABG Patients

RECOMMENDATIONS

CLASS I

1. Medical treatment for UA/NSTEMI patients after CABG should follow the same guidelines as for non–post-CABG patients with UA/NSTEMI. *(Level of Evidence: C)*
2. Because of the many anatomic possibilities that might be responsible for recurrent ischemia, there should be a low threshold for angiography in post-CABG patients with UA/NSTEMI. *(Level of Evidence: C)*

CLASS IIa

1. Repeat CABG is reasonable for UA/NSTEMI patients with multiple SVG stenoses, especially when there is significant stenosis of a graft that supplies the LAD. Percutaneous coronary intervention is reasonable for focal saphenous vein stenosis. *(Level of Evidence: C)* (Note that an intervention on a native vessel is generally preferable to that on a vein graft that supplies the same territory, if possible.)
2. Stress testing with imaging in UA/NSTEMI post-CABG patients is reasonable. *(Level of Evidence: C)*

Overall, up to 20% of patients presenting with UA/NSTEMI have previously undergone CABG (785). Conversely, approximately 20% of post-CABG patients develop UA/NSTEMI during an interval of 7.5 years (815), with a highly variable postoperative time of occurrence (816). Post-CABG patients who present with UA/NSTEMI are at higher risk, with more extensive CAD and LV dysfunction than those patients who have not previously undergone surgery.

6.3.1. Pathological Findings

Pathologically, intimal hyperplasia or atherosclerosis may develop in SVGs, and there is a particular tendency for thrombotic lesions to develop in these vessels (in 72% of grafts resected in 1 study) (817–820). In addition, post-CABG patients may develop atherosclerosis in their native vessels, and this can lead to UA/NSTEMI (820,821). However, obstructive lesions are more likely to occur in SVGs (53% within 5 years, 76% at 5 to 10 years, and 92% at greater than 10 years) (822), and there is a high rate of early graft failure in current practice (occlusion in up to one third at 1 year). Spasm in grafts or native vessels (823,824) and technical complications may also play a role in the development of UA/NSTEMI during the early postoperative period (815,825). Both angioscopic and angiographic findings indicate that SVG disease is a serious and unstable process. Angioscopically, friable plaques occur uniquely in SVGs (44% vs. 0% in native coronary arteries), whereas rough and white plaques occur in both SVGs and native coronary arteries (826). Angiographically, the SVGs more frequently have complex lesions (i.e., overhanging edges, irregular borders, ulcerations, or thrombosis), thrombi (37% vs. 12%, $p = 0.04$), and total occlusions (49% vs. 24%, $p = 0.02$) (822).

6.3.2. Clinical Findings and Approach

Compared with UA/NSTEMI patients without prior CABG, post-CABG patients are more often male (presumably because more men than women have undergone CABG), older, and more likely to have diabetes. They have more extensive native-vessel CAD and more previous MIs and LV dysfunction. Symptomatically, these patients have more prolonged chest pain than ACS patients without prior CABG. More than 30% of post-CABG patients have resting ECG abnormalities, and ECG stress tests are therefore less conclusive (827); however, a test that becomes positive after having been negative is helpful in the diagnosis of ischemia. Myocardial stress perfusion imaging and dobutamine echocardiography are often helpful diagnostically (828). Furthermore, a positive imaging test can help to

define the area of ischemia in post-CABG patients with complex disease.

The outcomes of UA/NSTEMI in post-CABG patients are less favorable than those in patients who have not undergone CABG. There is a high rate of embolization of atherosclerotic material from friable grafts at the time of intervention, which makes these procedures more difficult and which is associated with higher rates of complications (829). In one matched case-control study of UA, the initial course was similar, but post-CABG patients had twice the incidence of adverse events (death, MI, or recurrent UA) during the first year. This was attributed to a lower rate of complete revascularization, which was possible in only 9 of 42 post-CABG patients compared with 39 of 52 patients who had not previously undergone CABG ($p = 0.001$) (815). Results were directionally similar in the TIMI III registry of ACS, in which 16% of patients were post-CABG. Here again, early outcomes in post-CABG patients and others were equivalent, but at 1 year, the rate of adverse events (death, MI, or recurrent ischemia) was 39.3% for those who had previously undergone CABG versus 30.2% for those who had not ($p = 0.002$) (830).

Revascularization with either PCI or reoperation often is indicated and is possible in post-CABG patients with UA/NSTEMI. In a randomized controlled trial that compared stents with PTCA of obstructed SVGs, there was no statistically significant difference in restenosis during a 6-month period, although a trend favored stents (34% vs. 46%) (831). Although hemorrhagic complications were higher in the stent group, clinical outcomes (freedom from MI or repeat revascularization) were better (73% vs. 58%, $p = 0.03$) (831).

6.3.3. Conclusions

Post-CABG patients, especially those with only SVGs, are at high risk of UA/NSTEMI. There is a higher likelihood of disease in SVGs than in native arteries, and this difference increases with postoperative time. Pathologically and angiographically, disease in SVGs has characteristics associated with instability. There also are difficulties with treadmill ECG testing and less favorable outcomes with repeat revascularization than in patients who have not undergone previous CABG.

6.4. Older Adults

RECOMMENDATIONS

CLASS I

1. **Older patients with UA/NSTEMI should be evaluated for appropriate acute and long-term therapeutic interventions in a similar manner as younger patients with UA/NSTEMI. *(Level of Evidence: A)***
2. **Decisions on management of older patients with UA/NSTEMI should not be based solely on chronologic age but should be patient-centered, with consideration given to general health, functional and cognitive status, comorbidities, life expectancy, and patient preferences and goals. *(Level of Evidence: B)***
3. **Attention should be given to appropriate dosing (i.e., adjusted by weight and estimated creatinine clearance) of pharmacological agents in older patients with UA/NSTEMI, because they often have altered pharmacokinetics (due to reduced muscle mass, renal and/or hepatic dysfunction, and reduced volume of distribution) and pharmacodynamics (increased risks of hypotension and bleeding). *(Level of Evidence: B)***
4. **Older UA/NSTEMI patients face increased early procedural risks with revascularization relative to younger patients, yet the overall benefits from invasive strategies are equal to or perhaps greater in older adults and are recommended. *(Level of Evidence: B)***
5. **Consideration should be given to patient and family preferences, quality-of-life issues, end-of-life preferences, and sociocultural differences in older patients with UA/NSTEMI. *(Level of Evidence: C)***

Older adults represent a group of patients in whom baseline risk is higher (Table 25) and who have more comorbidities but who derive equivalent or greater benefit (e.g., invasive vs. conservative strategy) compared to younger patients. Although a precise definition of "older patients" or "elderly" has not been established in the medical literature, many studies have used this term to refer to those who are 75 years and older. On the basis of a large national ACS registry, older patients make up a substantial portion of those presenting with UA/NSTEMI, with 35% older than 75 years and 11% aged more than 85 years (832). Older persons also present with a number of special and complex challenges. First, older persons who develop UA/NSTEMI are more likely to present with atypical symptoms, including dyspnea and

Table 25. Impact of Age on Outcomes of Acute Coronary Syndrome: GRACE Risk Model

Age Group	No. of Deaths (Hospital Mortality Rate)*	Crude OR (95% CI)	Adjusted OR (95% CI)
Less than 45 y	20 (1.3)	Reference	Reference
45 to 54 y	79 (2.0)	1.47 (0.90 to 2.41)	1.95 (1.06 to 3.61)
55 to 64 y	171 (3.1)	2.35 (1.47 to 3.74)	2.77 (1.53 to 4.99)
65 to 74 y	373 (5.5)	4.34 (2.76 to 6.83)	4.95 (2.78 to 8.79)
75 to 84 y	439 (9.3)	7.54 (4.80 to 11.8)	8.04 (4.53 to 14.3)
85 y or more	260 (18.4)	16.7 (10.5 to 26.4)	15.7 (8.77 to 28.3)

*All p less than 0.0001. The GRACE risk model includes systolic blood pressure, initial serum creatinine, heart rate, initial cardiac enzyme, Killip class, ST- segment deviation, and cardiac arrest at hospital arrival. Modified with permission from Avezum A, Makdisse M, Spencer F, et al. Impact of age on management and outcome of acute coronary syndrome: observations from the Global Registry of Acute Coronary Events (GRACE). Am Heart J 2005; 149:67–73 (835).

CI = confidence interval; GRACE = Global Registry of Acute Coronary Events; OR = odds ratio.

confusion, rather than with the chest pain typically experienced by younger patients with acute myocardial ischemia (833). Conversely, noncardiac comorbidities such as chronic obstructive lung disease, gastroesophageal reflux disease, upper-body musculoskeletal symptoms, pulmonary embolism, and pneumonia also are more frequent and may be associated with chest pain at rest that can mimic classic symptoms of UA/NSTEMI. Hence, successful recognition of true myocardial ischemia in the elderly is often more difficult than in younger patients. Second, they are more likely than younger patients to have altered or abnormal cardiovascular anatomy and physiology, including a diminished beta-sympathetic response, increased cardiac afterload due to decreased arterial compliance and arterial hypertension, orthostatic hypotension, cardiac hypertrophy, and ventricular dysfunction, especially diastolic dysfunction (834). Third, older patients typically have developed significant cardiac comorbidities and risk factors, such as hypertension, prior MI, HF, cardiac conduction abnormalities, prior CABG, peripheral and cerebrovascular disease, diabetes mellitus, renal insufficiency, and stroke. Fourth, because of this larger burden of comorbid disease, older patients tend to be treated with a greater number of medications and are at higher risk for drug interactions and polypharmacy. Hence, among an already high-risk population, older age is associated with higher disease severity and higher disease and treatment risk at presentation (832).

6.4.1. Pharmacological Management

Overall, although the elderly have been generally underrepresented in randomized controlled trials, when examined, older subgroups appear to have relatively similar relative risk reductions and similar or greater absolute risk reductions in many end points as younger patients for commonly used treatments in the management of UA/NSTEMI. In spite of an increasing number of possible relative contraindications associated with older age, the rates of serious adverse events for most older patients generally remain low when evidence-based treatment for UA/NSTEMI is provided. Despite generally similar benefits, recent studies such as CRUSADE (832), TACTICS-TIMI 18 (182), and GRACE (835) have documented significantly lower use of evidence-based therapies in the elderly, including less use of an aggressive, early invasive strategy and of key pharmacotherapies, including anticoagulants, beta blockers, clopidogrel, and GP IIb/IIIa inhibitors.

With this said, precautions need to be taken to personalize these therapies (i.e., beginning with lower doses than in younger patients, whenever appropriate, and providing careful observation for toxicity). Older persons are particularly vulnerable to adverse events from cardiovascular drugs due to altered drug metabolism and distribution, as well as to exaggerated drug effects. Reductions in cardiac output and in renal and hepatic perfusion and function decrease the rate of elimination of drugs in the elderly. Additionally, older patients typically have lower drug distribution volumes (due to a lower body mass). As a result, drugs need to be carefully selected and individually adjusted. Current evidence demonstrates that older adults are frequently excessively dosed. In a community-based registry, among treated patients aged 75 years or older, 38% received an excessive dose of UFH, 17% received excessive LMWH, and 65% received an excessive dose of a GP IIb/IIIa antagonist (832). A subsequent study from the same registry found that 15% of major bleeding in UA/NSTEMI patients could be attributed to excessive dosing (743). Mortality and length of stay also were higher in patients receiving excessive dosing.

In the elderly, drugs such as beta blockers that undergo first-pass hepatic metabolism exhibit increased bioavailability (836). Exaggerated pharmacodynamic responses to drugs often resulted from lower cardiac output, plasma volume, and vasomotor tone, as well as blunted baroreceptor and beta-adrenergic responses.

6.4.2. Functional Studies

Older persons can have difficulty performing standardized exercise tolerance tests because of age-related medical problems, such as general deconditioning, decreased lung capacity, chronic pain, sensory neuropathy, osteoarthritis, and muscle weakness. Furthermore, the higher prevalence of preexisting resting ECG abnormalities (782), arrhythmias (140,837), and cardiac hypertrophy often make the interpretation of a standard stress ECG inconclusive or impossible. In such patients, alternative methods for evoking evidence of acute myocardial ischemia, such as pharmacological stress testing with dynamic cardiac imaging, may be substituted (see also Section 3.4).

6.4.3. Percutaneous Coronary Intervention in Older Patients

Recent evidence from several major interventional trials has demonstrated a clear benefit for older patients. A collaborative meta-analysis of several more recently published PCI trials (FRISC-II, TACTICS, RITA-3, VINO, and MATE) have suggested that the majority of the benefit from an invasive strategy in the elderly has accrued from contemporary strategies used in trials published after 1999 and in patients with positive troponins or their cardiac biomarkers (543). These trials indicated that compared with younger patients, the elderly gain important absolute benefits from an early invasive strategy but at a cost of increased bleeding. Specifically, a significant benefit was seen in reduction of the combined end point of death and recurrent MI, but only a trend to reduction in death was noted. A recent observational analysis in a community population failed to show an early benefit on in-hospital survival with an invasive strategy in the older subgroup (75 years or older), which highlights the need for continued caution in applying trial results uniformly in older patients (837a). Thus, selection of older patients for an early invasive strategy is complex, including risk from disease and risk

from intervention, but given the absolute benefits observed in these trials, age should not preclude consideration.

Despite these potential benefits, older patients are also far less likely to undergo angiography (RR 0.65, p less than 0.001 at 6 weeks) and coronary revascularization (RR 0.79, $p = 0.002$ at 6 weeks) after a UA/NSTEMI episode than younger patients. This apparent underuse of potentially beneficial interventions might be due in part to practitioner concerns about the increased risk of complications. Finding the appropriate balance between benefit and risk of aggressive therapies to maximize net clinical outcome remains a challenge in the elderly.

6.4.4. Contemporary Revascularization Strategies in Older Patients

Several studies of PCI in patients aged 65 to 75 years have shown that success rates with experienced medical professionals are similar to those in younger patients, but with even older patients, success rates decline and complication rates rise. On the other hand, a Mayo Clinic review of PCI in patients greater than 65 years old (of whom 75% had UA) revealed an overall success rate of 93.5%, an immediate in-hospital mortality rate of 1.4%, and a need for emergency CABG rate of only 0.7% (838). Angiographic outcome changed little between the 65-to-69-year-old group and the greater than 75-year-old group, and the 1-year event rate (death, MI, CABG, repeat PCI, or severe angina) was 45.1% in all patients greater than 65 years old (838). Predictors of outcomes (i.e., extent and severity of CAD and comorbidities) after PCI in older patients were the same as those in younger patients (839). Similarly, a review of coronary stenting in the elderly reported that procedural success rates were high (95% to 98%) and periprocedural complication rates were low (MI 1.2% to 2.8%, urgent CABG 0.9% to 1.8%, repeat PCI 0% to 0.6%) in the elderly, with little difference between those greater than 75 years old and those less than 65 years old (840). Subgroup analyses in both TIMI IIIB (129) and FRISC-II (245) showed a greater advantage of the invasive strategy in patients older than 65 years of age. More contemporary studies have confirmed this advantage, including TACTICS-TIMI 18 (841). Among patients older than 75 years of age, the early invasive strategy conferred an absolute reduction of 10.8 percentage points (to 10.8% from 21.6%; $p = 0.016$) and a relative reduction of 56% in death or MI at 6 months; however, benefits came with an increased risk of major bleeding events (16.6% vs. 6.5%; $p = 0.009$).

A review of 15,679 CABG procedures performed in patients greater than 70 years old from the Toronto Hospital (842) reported encouraging results. Operative mortality rates declined from 7.2% in 1982 to 1986, to 4.4% in 1987 to 1991 (and from 17.2% to 9.1% for high-risk patients) but showed little further change in the period of 1992 to 1996. Predictors of operative death (LV dysfunction, previous CABG, peripheral vascular disease, and diabetes) were similar to those in younger patients.

Operative morbidity and mortality rates increase for CABG with advanced age, but outcomes have been favorable compared with medical therapy, and quality of life improves (843–847). A recent retrospective review of 662,033 patients who underwent cardiac surgical procedures performed using the STS National Cardiac Database (848) found a CABG operative mortality of 2.8% for patients 50 to 79 years of age, 7.1% for patients 80 to 89 years of age, and 11.8% for patients aged 90 years or more. This study included more than 1,000 patients over 90 years of age and 5 centenarians and documented that the 57% of nonagenarians without certain risk factors (renal failure, IABP, emergency surgery, or peripheral or cerebrovascular disease) constituted a relatively low-risk group with an operative mortality of only 7.2%, similar to the overall risk in octogenarians. Thus, with appropriate selection, CABG surgery can be an appropriate revascularization strategy in even the oldest patient subgroups.

6.4.5. Conclusions

Older patients with UA/NSTEMI tend to have atypical presentations of disease, substantial comorbidity, ECG stress tests that are more difficult to interpret, and different physiological responses to pharmacological agents compared with younger patients. Although they are at highest risk, guideline-recommended therapies are used less frequently. Even though their outcomes with interventions and surgery are not as favorable as those of younger patients, coronary revascularization should be recommended when the same group of prognostic risk factors that play a role in the younger age group are taken into account. The approach to these patients also must consider general medical and cognitive status, bleeding risk and other risk of interventions, anticipated life expectancy, and patient or family preferences.

6.5. Chronic Kidney Disease

RECOMMENDATIONS

CLASS I

1. **Creatinine clearance should be estimated in UA/NSTEMI patients, and the doses of renally cleared drugs should be adjusted appropriately. *(Level of Evidence: B)***
2. **In chronic kidney disease patients undergoing angiography, isosmolar contrast agents are indicated and are preferred. *(Level of Evidence: A)***

Chronic kidney disease (CKD) is not only a coronary risk equivalent for ascertainment of coronary risk but also a risk factor for the development and progression of CVD (744). Chronic kidney disease constitutes a risk factor for adverse outcomes after MI (849), including NSTEMI and other coronary patient subsets. In the highly validated GRACE risk score, serum creatinine is 1 of the 8 independent predictors of death (168,835). In recent study, even early CKD constituted a significant risk factor for cardiovascular events and death (849,850). Chronic kidney disease also predicts an increase in recurrent cardiovascular events (851). Cardiovascular death is 10 to 30 times higher in dialysis

patients than in the general population. The underrepresentation of patients with renal disease in randomized controlled trials of CVD is of concern (179). Most of the limited evidence available and current opinion suggest that when appropriately monitored, cardiovascular medications and interventional strategies can be applied safely in those with renal impairment and provide therapeutic benefit (849). However, not all recent evidence is consistent with this premise: atorvastatin did not significantly reduce the primary end point of cardiovascular death, nonfatal MI, or stroke in a prospective randomized trial of patients with diabetes and end-stage CKD who were undergoing hemodialysis (234). The preference for primary PCI has also been questioned (235).

Particularly in the setting of ACS, bleeding complications are higher in this patient subgroup because of platelet dysfunction and dosing errors; benefits of fibrinolytic therapy, antiplatelet agents, and anticoagulants can be negated or outweighed by bleeding complications; and renin-angiotensin-aldosterone inhibitors can impose a greater risk because of the complications of hyperkalemia and worsening renal function in the CKD patient. Angiography carries an increased risk of contrast-induced nephropathy; the usual benefits of percutaneous interventions can be lessened or abolished; and PCI in patients with CKD is associated with a higher rate of early and late complications of bleeding, restenosis, and death (179). Thus, the identification of CKD is important in that it represents an ACS subgroup with a far more adverse prognosis but for whom interventions have less certain benefit.

Coronary arteriography is a frequent component of the care of ACS patients. As such, contrast-induced nephropathy can constitute a serious complication of diagnostic and interventional procedures. In patients with CKD or CKD and diabetes, isosmolar contrast material lessens the rise in creatinine and is associated with lower rates of contrast-induced nephropathy than low-osmolar contrast media. This has been documented in a randomized clinical trial (RECOVER [Renal Toxicity Evaluation and Comparison Between Visipaque (Iodixanol) and Hexabrix (Ioxaglate) in Patients With Renal Insufficiency Undergoing Coronary Angiography]) comparing iodixanol with ioxaglate (852) and in a meta-analysis of 2,727 patients from 16 randomized clinical trials (853). Identification of CKD patients as recommended in the AHA science advisory on detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease should guide the use of isosmolar contrast agents (744).

To increase awareness of CKD, an AHA science advisory for the detection of CKD in patients with or at increased risk for CVD recently was developed in collaboration with the National Kidney Foundation (744). The advisory recommendations are that all patients with CVD be screened for evidence of kidney disease by estimating glomerular filtration rate, testing for microalbuminuria, and measuring the albumin-to-creatinine ratio (Class IIa, Level of Evidence: C). A glomerular filtration rate less than 60 ml per min per 1.73 square meters of body surface should be regarded as abnormal (Class I, Level of Evidence: B). Furthermore, the albumin-to-creatinine ratio should be used to screen for the presence of kidney damage in adult patients with CVD, with values greater than 30 mg of albumin per 1 g of creatinine regarded as abnormal (Class IIa, Level of Evidence: B).

A diagnosis of renal dysfunction is critical to proper medical therapy of UA/NSTEMI. Many cardiovascular drugs used in UA/NSTEMI patients are renally cleared; their doses should be adjusted for estimated creatinine clearance (see also Section 3). In a large community-based registry study, 42% of patients with UA/NSTEMI received excessive initial dosing of at least 1 antiplatelet or antithrombin agent (UFH, LMWH, or GP IIb/IIIa inhibitor) (743). Renal insufficiency was an independent predictor of excessive dosing. Dosing errors predicted an increased risk of major bleeding. Clinical studies and labeling that defines adjustments for several of these drugs have been based on the Cockroft-Gault formula for estimating creatinine clearance, which is not identical to the MDRD formula. Use of the Cockroft-Gault formula to generate dose adjustments is recommended. The impact of renal dysfunction on biomarkers of necrosis (i.e., troponin) is discussed in Section 2.2.8.2.1.

To increase the meager evidence base and to optimize care for this growing high-risk population, the recognition of CKD patients with or at risk of CVD and the inclusion and reporting of renal disease in large CVD trials must be increased in the future.

6.6. Cocaine and Methamphetamine Users

RECOMMENDATIONS

CLASS I

1. Administration of sublingual or intravenous NTG and intravenous or oral calcium channel blockers is recommended for patients with ST-segment elevation or depression that accompanies ischemic chest discomfort after cocaine use. *(Level of Evidence: C)*
2. Immediate coronary angiography, if possible, should be performed in patients with ischemic chest discomfort after cocaine use whose ST segments remain elevated after NTG and calcium channel blockers; PCI is recommended if occlusive thrombus is detected. *(Level of Evidence: C)*
3. Fibrinolytic therapy is useful in patients with ischemic chest discomfort after cocaine use if ST segments remain elevated despite NTG and calcium channel blockers, if there are no contraindications, and if coronary angiography is not possible. *(Level of Evidence: C)*

CLASS IIa

1. Administration of NTG or oral calcium channel blockers can be beneficial for patients with normal ECGs or minimal ST-segment deviation suggestive of ischemia after cocaine use. *(Level of Evidence: C)*
2. Coronary angiography, if available, is probably recommended for patients with ischemic chest discomfort after cocaine use with ST-segment depression or isolated T-wave changes not known to be previously present and who are unresponsive to NTG and calcium channel blockers. *(Level of Evidence: C)*
3. Management of UA/NSTEMI patients with methamphetamine use similar to that of patients with cocaine use is reasonable. *(Level of Evidence: C)*

CLASS IIb

Administration of combined alpha- and beta-blocking agents (e.g., labetalol) may be reasonable for patients after cocaine use with hypertension (systolic blood pressure greater than 150 mm Hg) or those with sinus tachycardia (pulse greater than 100 beats per min) provided that the patient has received a vasodilator, such as NTG or a calcium channel blocker, within close temporal proximity (i.e., within the previous hour). *(Level of Evidence: C)*

CLASS III

Coronary angiography is not recommended in patients with chest pain after cocaine use without ST-segment or T-wave changes and with a negative stress test and cardiac biomarkers. *(Level of Evidence: C)*

The use of cocaine can produce myocardial ischemia, thereby leading to UA/NSTEMI (854–857). The widespread use of cocaine makes it mandatory to consider this cause, because its recognition mandates special management. Specifically, initial management recommendations for cocaine-induced ACS include NTG and calcium channel antagonists. Assessment for resolution of chest discomfort and ECG changes is then undertaken before fibrinolytic therapy is initiated or angiography is considered. The use of beta blockers in close proximity (i.e., within 4 to 6 h) of cocaine exposure is controversial, with some evidence for harm; thus, when used, the guidelines recommend combination alpha and beta blockade in addition to a vasodilator. There are no data to guide recommendations for beta blockade later after exposure, after cocaine elimination.

The action of cocaine is to block presynaptic reuptake of neurotransmitters such as norepinephrine and dopamine, which produces excess concentrations at the postsynaptic receptors that lead to sympathetic activation and the stimulation of dopaminergic neurons (858). There may also be a direct contractile effect on vascular smooth muscle (855). Detoxification is accomplished with plasma and liver cholinesterases, which form metabolic products that are excreted in the urine. Infants, elderly patients, and patients with hepatic dysfunction lack sufficient plasma cholinesterase to metabolize the drug (859) and therefore are at high risk of adverse effects with cocaine use.

6.6.1. Coronary Artery Spasm With Cocaine Use

The basis for coronary spasm has been demonstrated in both in vitro (859) and in vivo (855,860–864) experiments in animals and humans. Reversible vasoconstriction of rabbit aortic rings has been demonstrated with cocaine in concentrations of 10^{-3} to 10^{-8} mol per liter. Pretreatment with calcium channel blockers markedly inhibits cocaine-induced vasoconstriction. Coronary injection of cocaine produces vasoconstriction in miniswine with experimentally induced nonocclusive atherosclerotic lesions (865).

Nademanee et al. (866) performed 24-h ECG monitoring in 21 male cocaine users after admission to a substance abuse treatment center and found that 8 had frequent episodes of ST-segment elevation, most during the first 2 weeks of withdrawal. In cocaine users with prolonged myocardial ischemia, coronary arteriography can reveal coronary artery spasm with otherwise normal-appearing coronary arteries or with underlying minimally obstructive coronary atherosclerosis (855,857,860). The cocaine-induced increase in coronary vascular resistance is reversed with calcium channel blockers (861,867). Cocaine increases the response of platelets to arachidonic acid, thus increasing thromboxane A2 production and platelet aggregation (868). In addition, reversible combined reduction in protein C and antithrombin III has been observed in patients with cocaine-related arterial thrombosis (869). All of these effects favor coronary thrombosis (855,862,870). Coronary thrombosis can also develop as a consequence of coronary spasm.

Cocaine users can develop ischemic chest discomfort that is indistinguishable from the UA/NSTEMI secondary to coronary atherosclerosis. The patient who presents with prolonged myocardial ischemia should be questioned about the use of cocaine. In a study by Hollander et al. (871), the presence or absence of cocaine use was assessed in only 13% of patients who presented to the ED with chest pain. Table 26 lists the clinical characteristics of a typical patient with cocaine-related chest pain or MI (857).

Most patients who present to the ED with cocaine-associated chest pain do not develop MI (872). MI development has been reported to occur only in 6% of such patients (857).

Accelerated coronary atherosclerosis has been reported in chronic users of cocaine (873,874); coronary artery spasm is more readily precipitated at sites of atherosclerotic plaques (860). Cocaine causes sinus tachycardia, as well as an increase in blood pressure and myocardial contractility, thereby increasing myocardial oxygen demand (861). These increases can precipitate myocardial ischemia and UA/NSTEMI in both the presence and absence of obstructive coronary atherosclerosis and coronary spasm.

Aortic dissection (875) and coronary artery dissection (855,875) have been reported as consequences of cocaine use. Other reported cardiac complications are myocarditis (874) and cardiomyopathy (876,877).

Table 26. Clinical Characteristics in the Typical Patient With Cocaine-Related Chest Pain, Unstable Angina, or Myocardial Infarction

Young age, usually less than 40 years
Male gender
Cigarette smoker, but no other risk factors for atherosclerosis
Chronic or first-time cocaine user
Symptom onset minutes or even several hours after cocaine use
Associated with all routes of administration
May occur with small or large doses
Often associated with concomitant use of cigarettes and/or alcohol

Reprinted from Progressive Cardiovascular Disease, 40, Pitts WF, Lange RA, Cigarroa JE, Hillis LD. Cocaine-induced myocardial ischemia and infarction: pathophysiology, recognition, and management, 65–76. Copyright 1997, with permission from Elsevier (857).

6.6.2. Treatment

When a patient with or suspected of cocaine use is seen in the ED with chest pain compatible with myocardial ischemia and ST-segment elevation, sublingual NTG or a calcium channel blockers (e.g., diltiazem 20 mg IV) should be administered (855,864). If there is no response, immediate coronary angiography should be performed, if possible. Fibrinolytic therapy has been successfully employed in patients with MI after cocaine use, although these patients frequently have contraindications to fibrinolysis, including hypertension, seizures, or aortic dissection. Thus, PCI may be a preferred method of revascularization in this setting. However, even this therapeutic strategy is problematic in subjects with cocaine-related MI; those in whom stents are deployed are at substantial risk of subsequent in-stent thrombosis unless double-antiplatelet therapy (ASA and clopidogrel) is ingested regularly and predictably for several months afterward, and those who partake in substance abuse often are unreliable in adhering to such a regimen. Thus, bare-metal stents, which require a shorter duration of dual-antiplatelet therapy, generally are preferred to DES in cocaine abusers. If thrombus is present and PCI is unavailable or ineffective, fibrinolytic agents may be administered if there are no contraindications (878,879). If catheterization is not available, intravenous fibrinolytic therapy may be considered in patients with ST-segment elevation and clinical symptoms consistent with MI.

If the ECG is normal or shows only minimal T-wave changes and there is a history of chest pain compatible with acute myocardial ischemia, the patient should receive sublingual NTG or an oral calcium channel blocker and be observed. After cocaine use, increased motor activity, skeletal muscle injury, and rhabdomyolysis can occur, causing CK and even CK-MB elevation in the absence of MI (880). Troponin I and TnT are more specific for myocardial injury and therefore are preferred. Blood should be drawn twice for serum markers of myocardial necrosis at 6-h intervals. If the ECG shows ST-segment changes and the cardiac biochemical markers are normal, the patient should be observed in the hospital in a monitored bed for 24 h; most complications will occur within 24 h (881). If the patient's clinical condition is unchanged and the ECG remains unchanged after 24 h, the patient can be discharged (879). A shorter observation period of 9 to 12 h, with measurement of troponin levels at 3, 6, and 9 h after presentation, also has been validated (882).

Many observers believe that beta blockers are contraindicated in cocaine-induced coronary spasm because there is evidence from a single double-blind, randomized, placebo-controlled trial that beta-adrenergic blockade augments cocaine-induced coronary artery vasoconstriction (883). Others believe that if the patient has a high sympathetic state with sinus tachycardia and hypertension, beta blockers should be used (855). Labetalol, an alpha and beta blocker, has been advocated, because it has been shown not to induce coronary artery vasoconstriction (884) even though its beta-adrenergic–blocking action predominates over its alpha-adrenergic–blocking activity in the doses that are commonly used (884). Therefore, in cocaine-induced myocardial ischemia and vasoconstriction, NTG and calcium channel blockers are the preferred drugs. Both NTG and verapamil have been shown to reverse cocaine-induced hypertension, coronary arterial vasoconstriction (864,883), and tachycardia (verapamil).

6.6.3. Methamphetamine Use and UA/NSTEMI

Given the rapid increase in methamphetamine abuse, recognition of its cardiovascular risk is of mounting importance. Currently, the evidence base for UA/NSTEMI after methamphetamine and its treatment is limited to a few publications of case reports and small series (885–888). These suggest that ACS is increasingly common in patients evaluated in the ED for chest discomfort after methamphetamine use and that the frequency of other potentially life-threatening arrhythmias is not negligible (886). Clinical presentation resembles that of cocaine-associated ACS. On the basis of the similarities in pathophysiology and these few clinical observations, therapy similar to that of cocaine-induced UA/NSTEMI is recommended pending information more specific to methamphetamine.

6.7. Variant (Prinzmetal's) Angina

RECOMMENDATIONS

CLASS I

1. **Diagnostic investigation is indicated in patients with a clinical picture suggestive of coronary spasm, with investigation for the presence of transient myocardial ischemia and ST-segment elevation during chest pain.** ***(Level of Evidence: A)***
2. **Coronary angiography is recommended in patients with episodic chest pain accompanied by transient ST-segment elevation.** ***(Level of Evidence: B)***
3. **Treatment with nitrates and calcium channel blockers is recommended in patients with variant angina whose coronary angiogram shows no or nonobstructive coronary artery lesions. Risk factor modification is recommended, with patients with atherosclerotic lesions considered to be at higher risk.** ***(Level of Evidence: B)***

CLASS IIb

1. **Percutaneous coronary intervention may be considered in patients with chest pain and transient ST-segment elevation and a significant coronary artery stenosis.** ***(Level of Evidence: B)***
2. **Provocative testing may be considered in patients with no significant angiographic CAD and no documentation of transient ST-segment elevation when clinically relevant symptoms possibly explained by coronary artery spasm are present.** ***(Level of Evidence: C)***

CLASS III

Provocative testing is not recommended in patients with variant angina and high-grade obstructive stenosis on coronary angiography. ***(Level of Evidence: B)***

Variant angina (Prinzmetal's angina, periodic angina) is a form of UA that usually occurs spontaneously and is characterized by transient ST-segment elevation that spontaneously resolves or resolves with NTG use without progression to MI (889). The earliest stages of MI can also be associated with cyclic ST-segment elevations, but MI does not possess the

nature of periodic angina. The spasm is most commonly focal and can occur simultaneously at more than 1 site (890). Even coronary segments that are apparently normal on coronary angiography often have evidence of mural atherosclerosis on intravascular ultrasound (891). This can result in localized endothelial dysfunction and coronary spasm.

Patients with Prinzmetal's angina frequently have coronary artery plaques that can be either nonobstructive or obstructive (892). Walling et al. (893) reported that coronary arteriography showed 1-vessel disease in 81 (39%) of 217 patients and multivessel disease in 40 (19%). Rovai et al. (894) found a similar high prevalence of obstructive disease in 162 patients with variant angina.

6.7.1. Clinical Picture

Although chest discomfort in the patient with variant angina can be precipitated by exercise, it usually occurs without any preceding increase in myocardial oxygen demand; the majority of patients have normal exercise tolerance, and stress testing may be negative. Because the anginal discomfort usually occurs at rest without a precipitating cause, it may simulate UA/NSTEMI secondary to coronary atherosclerosis. Episodes of Prinzmetal's angina often occur in clusters, with prolonged asymptomatic periods of weeks to months. Attacks can be precipitated by an emotional stress, hyperventilation (895), exercise (896), or exposure to cold (897). A circadian variation in the episodes of angina is most often present, with most attacks occurring in the early morning (898). Compared with patients with chronic stable angina, patients with variant angina are younger and, except for smoking, have fewer coronary risk factors (899,900). Some studies have shown an association of variant angina with other vasospastic disorders, such as migraine headache and Raynaud's phenomenon (901). The presence of syncope during an episode of chest pain suggests severe ischemia related to an acute occlusion, often due to focal spasm.

Most often, the attacks of angina resolve spontaneously without evidence of MI. However, a prolonged vasospasm may result in complications such as MI, a high degree of AV block, life-threatening ventricular tachycardia, or sudden death (902,903).

6.7.2. Pathogenesis

The pathogenesis of focal coronary spasm in this condition is not well understood. The probable underlying defect is the presence of dysfunctional endothelium that exposes the medial smooth muscle to vasoconstrictors such as catecholamines, thromboxane A2, serotonin, histamine, and endothelin (904). Endothelial dysfunction also can impair coronary flow-dependent vasodilatation owing to the decreased production and release of nitric oxide (905) and enhanced phosphorylation of myosin light chains, an important step in smooth muscle contraction (906). There can be an imbalance between endothelium-produced vasodilator factors (i.e., prostacyclin, nitric oxide) and vasoconstrictor factors (i.e., endothelin, angiotensin II) that favors the latter (907). There also is evidence of involvement of the autonomic nervous system, with reduced parasympathetic tone and enhanced reactivity of the alpha-adrenergic vascular receptors (905,908,909). Regardless of the mechanism, the risk for focal spasm is transient but recurrent.

6.7.3. Diagnosis

The key to the diagnosis of variant angina is the documentation of ST-segment elevation in a patient during transient chest discomfort (which usually occurs at rest, typically in the early morning hours, and nonreproducibly during exercise) and that resolves when the chest discomfort abates. Typically, NTG is exquisitely effective in relieving the spasm. ST-segment elevation implies transmural focal ischemia associated with complete or near-complete coronary occlusion of an epicardial coronary artery in the absence of collateral circulation. In variant angina, the dynamic obstruction can be superimposed on severe or nonsevere coronary stenosis or supervene in an angiographically normal coronary artery segment. Hence, coronary angiography is usually part of the workup of these patients and can help orient treatment.

It is noteworthy that spasm often develops spontaneously during angiography, which aids the diagnosis in patients with no previously documented ST-segment elevation; catheter-induced spasm is not, however, an indicator of vasospastic disease. Diagnostic tests for Prinzmetal's angina are based on the recording of transient ST-segment elevation during an episode of chest pain. Continuous 12-lead ECG monitoring can be performed for this purpose in-hospital or as an outpatient; recording during numerous episodes of pain improves diagnostic sensitivity. A treadmill exercise test is also useful; one third of patients will show ST-segment elevation, another third ST-segment depression, and one third no ST-segment change. Interestingly, the results may not be reproducible within the same patients and are more often positive when the test is performed in the early morning hours. A 2-dimensional echocardiogram or the injection of a nuclear marker at the time of chest pain may help document the presence of transmural ischemia. A number of other provocative tests can be used to precipitate coronary artery spasm when the diagnosis is suspected but not objectively documented. Nitrates and calcium channel blockers should be withdrawn well before provocative testing. These tests are more often used during coronary angiography; the spasm can then be visualized before the appearance of chest pain and promptly relieved by the intracoronary injection of NTG. The test can also be performed in a coronary care unit setting while the patient is monitored for ST-segment elevation, but this is recommended only if the coronary anatomy is known. Such nonpharmacological tests include the cold pressor test and hyperventilation performed for 6 min in the morning, alone or after exercise (910). Pharmacological tests in general provide a better diagnostic yield. Ergonovine, methylergonovine, and ergometrin have been most widely studied and used in the past, but methylergonovine and ergometrin are no longer generally available, and

the use of ergonovine is limited. Acetylcholine and methacholine are now predominantly used for this diagnostic purpose. Although the spasm is usually promptly relieved with NTG administered intracoronarily or intravenously, it may at times be refractory to therapy with NTG and other vasodilators and may be recurrent in the same segment or in other coronary artery segments, resulting in prolonged ischemia, MI, or occasionally, death (911). For these reasons, provocative tests are now rarely used and are limited to a few indications, such as patients with suggestive symptoms that could be helped by an appropriate diagnosis not otherwise reached, patients in whom treatment with nitrates and calcium channel blockers has failed, and patients with a life-threatening disease in whom the physician wants to verify the efficacy of the treatment. Thus, patients with a positive hyperventilation test are more likely to have a higher frequency of attacks, multivessel spasm, or high degree of AV block or ventricular tachycardia than are patients with a negative hyperventilation test (910), and high-risk patients whose tests become negative with treatment are more likely to have a favorable long-term course. The investigation of coronary spasm in patients with coronary artery lesions of borderline significance can be complemented by other diagnostic procedures such as intravascular ultrasound, functional flow reverse, and other functional testing to assess more accurately the significance of the obstruction.

6.7.4. Treatment

Coronary spasm is usually very responsive to NTG, long-acting nitrates, and calcium channel blockers (912–914), which are considered first-line therapies. (Beta-blockers have theoretical adverse potential, and their clinical effect is controversial.) Smoking should be discontinued. Usually, a calcium channel blocker in a moderate to high dose (e.g., verapamil 240 to 480 mg per d, diltiazem 180 to 360 mg per d, or nifedipine 60 to 120 mg per d) is started; patients with very active disease can require a combination of nitrates and 2 calcium channel blockers of different classes (i.e., a dihydropyridine with verapamil or diltiazem). Alpha-receptor blockers have been reported to be of benefit, especially in patients who are not responding completely to calcium channel blockers and nitrates (906). In patients who develop coronary spasm (with or without provocation) during coronary angiography, 0.3 mg of NTG should be infused directly into the coronary artery that is involved.

6.7.5. Prognosis

The prognosis of variant angina is usually excellent in patients with variant angina who receive medical therapy, especially in patients with normal or near-normal coronary arteries. Yasue et al. (915) reported an 89% to 97% overall 5-year survival rate. In a 7-year follow-up in approximately 300 patients, the incidence of sudden death was 3.6% and the incidence of MI was 6.5% (915). Patients with coronary artery vasospasm superimposed on a fixed obstructive CAD have a worse prognosis. In a study of 162 patients with variant angina by Rovai et al. (894), patients with normal coronary arteries and single-vessel disease had a 5-year survival rate of 95% compared with a rate of 80% for those with multivessel disease. Almost identical survival rates were reported in an earlier study by Walling et al. (893). Occasional patients may require instrumentation with a pacemaker to prevent transient AV block associated with ischemia or with a defibrillator to prevent sudden death associated with ischemia-induced ventricular fibrillation. Treatment can at times be very frustrating in the occasional patient refractory to standard medication. Cardiac denervation has been used in these patients with marginal benefit.

6.8. Cardiovascular "Syndrome X"

RECOMMENDATIONS

CLASS I

1. Medical therapy with nitrates, beta blockers, and calcium channel blockers, alone or in combination, is recommended in patients with cardiovascular syndrome X. *(Level of Evidence: B)*
2. Risk factor reduction is recommended in patients with cardiovascular syndrome X. *(Level of Evidence: B)*

CLASS IIb

1. Intracoronary ultrasound to assess the extent of atherosclerosis and rule out missed obstructive lesions may be considered in patients with syndrome X. *(Level of Evidence: B)*
2. If no ECGs during chest pain are available and coronary spasm cannot be ruled out, coronary angiography and provocative testing with acetylcholine, adenosine, or methacholine and 24-h ambulatory ECG may be considered. *(Level of Evidence: C)*
3. If coronary angiography is performed and does not reveal a cause of chest discomfort, and if syndrome X is suspected, invasive physiological assessment (i.e., coronary flow reserve measurement) may be considered. *(Level of Evidence: C)*
4. Imipramine or aminophylline may be considered in patients with syndrome X for continued pain despite implementation of Class I measures. *(Level of Evidence: C)*
5. Transcutaneous electrical nerve stimulation and spinal cord stimulation for continued pain despite the implementation of Class I measures may be considered for patients with syndrome X. *(Level of Evidence: B)*

CLASS III

Medical therapy with nitrates, beta blockers, and calcium channel blockers for patients with noncardiac chest pain is not recommended. *(Level of Evidence: C)*

6.8.1. Definition and Clinical Picture

Cardiovascular "syndrome X" refers to patients with angina or angina-like discomfort with exercise, ST-segment depression on exercise testing, and normal or nonobstructed coronary arteries on arteriography (916). This entity should be differentiated from the metabolic syndrome X (metabolic syndrome), which describes patients with insulin resistance, hyperinsulinemia, dyslipidemia, hypertension, and abdominal obesity. It also should be differentiated from noncardiac chest pain. Syndrome X is more common in women than in men (679,916–918). Chest pain can vary from that of typical angina pectoris to chest pain with atypical features to

chest pain that simulates UA secondary to CAD (917). Other atypical features can be prolonged chest pain at rest and chest pain that is unresponsive to NTG (919). Most often, the chest pain occurs with activity and simulates angina pectoris due to stable CAD. However, because chest pain can accelerate in frequency or intensity or may occur at rest, the patient can present with the clinical picture of UA. Therefore, this syndrome is discussed in this guideline.

The cause of the discomfort and ST-segment depression in patients with syndrome X is not well understood. The most frequently proposed causes are impaired endothelium-dependent arterial vasodilatation with decreased nitric oxide production, impaired microvascular dilation (non–endothelium-dependent), increased sensitivity to sympathetic stimulation, or coronary vasoconstriction in response to exercise (731,920,921). Increased levels of plasma endothelin correlate with impaired coronary microvascular dilation (922). There is increasing evidence that these patients frequently also have an increased responsiveness to pain and an abnormality in pain perception.

The diagnosis of syndrome X is suggested by the triad of anginal-type chest discomfort, objective evidence of ischemia, and absence of obstructive CAD. The diagnosis can be confirmed by provocative coronary angiographic testing with acetylcholine for coronary endothelium-dependent function and adenosine for non–endothelium-dependent microvascular function. Other causes of angina-like chest discomfort not associated with cardiac disease, such as esophageal dysmotility, fibromyalgia, and costochondritis, must also be eliminated. In addition, in patients with a clinical presentation consistent with variant angina, coronary spasm must be ruled out by the absence of ST-segment elevation with the anginal discomfort or by provocative testing. Myocardial perfusion scanning may be abnormal owing to a patchy abnormal response to exercise of the microvasculature that can lead to reduced coronary flow to different regions of the myocardium (731). Magnetic resonance imaging studies also may suggest myocardial ischemia (923,924).

The intermediate-term prognosis of patients with syndrome X has been reported to be excellent in older studies (917,919,925). The CASS registry reported a 96% 7-year survival rate in patients with anginal-type chest pain, normal coronary arteriograms, and an LVEF greater than 0.50 (926). However, testing for ischemia was not performed in CASS. More recent data from WISE indicate that the prognosis in syndrome X, validated by ischemia testing, is not entirely benign with respect to risk of cardiac death and nonfatal MI (918,919). The WISE data demonstrate that the prognosis is related to the extent of angiographic disease across the range of 20% stenosis to obstructive lesions (918). Long-term follow-up shows that ventricular function usually remains normal (919), although there have been reports of progressive LV dysfunction, and many patients continue to have chest pain that requires medication (927).

Additional data from WISE (733,767–774) suggest adverse outcomes in some women with myocardial ischemia on noninvasive testing and nonobstructive CAD. A number of variables may be contributory. Intramural lesions, evidence of an atherosclerotic burden, are evident on intravascular ultrasound. A decrease in coronary flow reserve appears to independently predict major coronary events. In addition, there is important coronary endothelial dysfunction that may be related to hormonal influences, inflammatory markers, or oxidative stress and possibly to a clustering of risk factors as is seen in the metabolic syndrome. Other microvascular dysfunction may be present. Although half of the WISE women with myocardial ischemia documented on noninvasive testing had no flow-limiting coronary obstructive disease at angiography, not only were there persisting symptoms, but there was a subsequent significant occurrence of coronary events. Evaluation of the 4-year risk-adjusted freedom from death or MI showed that women with no or minimal obstructive disease had a total rate of occurrence of these end points of 9.4% by 4 years. Pending additional data, aggressive coronary risk factor reduction appears to be appropriate.

6.8.2. Treatment

Persistence of symptoms is common, and many patients do not return to work (919). The demonstration of normal coronary arteries on angiography can be reassuring. In 1 study, after a normal coronary arteriogram, there was a reduced need for hospitalization and a reduction in the number of hospital days for cardiac reasons (566). However, even minimal atherosclerotic disease on angiography warrants risk factor modification.

Both beta blockers and calcium channel blockers have been found to be effective in reducing the number of episodes of chest discomfort (928,929). Beneficial effects with nitrates are seen in approximately one half of patients (930). The use of alpha-adrenergic blockers would appear to be a rational therapy, but the results of small trials are inconsistent (931). Imipramine 50 mg daily has been successful in some chronic pain syndromes, including syndrome X, reducing the frequency of chest pain by 50% (932). Transcutaneous electrical nerve stimulation and spinal cord stimulation can offer good pain control (933,934). Estrogen in postmenopausal women with angina and normal coronary arteriograms has been shown to reverse the acetylcholine-induced coronary arterial vasoconstriction, presumably by improving endothelium-dependent coronary vasomotion (935), and to reduce the frequency of chest pain episodes by 50% (936). However, because of increased cardiovascular and other risks documented in randomized controlled trials of primary and secondary coronary prevention, hormone therapy is not recommended for chronic conditions (29). Statin therapy and exercise training have improved exercise capacity, endothelial function, and symptoms (937,938).

It is recommended that patients be reassured of the excellent intermediate-term prognosis and treated with long-acting nitrates. If the patient continues to have episodes of chest pain, a calcium channel blocker or beta blocker can be started (929). Finally, 50 mg of imipramine daily has been successful in

reducing the frequency of chest pain episodes (932). Cognitive behavioral therapy can be beneficial (939). If symptoms persist, other causes of chest pain, especially esophageal dysmotility, should be ruled out.

6.9. Takotsubo Cardiomyopathy

A disorder, or group of disorders, with several names (stress-induced cardiomyopathy, transient LV apical ballooning, Takotsubo cardiomyopathy, and broken heart syndrome) is an uncommon but increasingly reported cause of ACS. Takotsubo cardiomyopathy is noteworthy for the absence of obstructive coronary artery disease, typical precipitation by intense psychological or emotional stress, and predominant occurrence in postmenopausal women. The characteristic finding of apical LV ballooning is seen on left ventriculography or echocardiography, with transient ST elevation or deep T-wave inversions on the surface ECG. Despite the presence of positive cardiac biomarkers and frequent hemodynamic compromise or even cardiogenic shock, almost all patients recover completely, typically with normal wall motion within 1 to 4 weeks (730,940,941).

7. Conclusions and Future Directions

The last quarter century has witnessed enormous strides in the understanding of ACS pathophysiology and its management. These have included the critical role of coronary thrombosis (942), the novel concept and suggestion of a therapeutic benefit of reperfusion therapy (943–946), and finally, the demonstration of mortality reductions with fibrinolysis in large, multicenter trials (531a). However, these trials also uncovered the paradox that fibrinolysis did not benefit or even harmed NSTEMI patients (531a). This central management dichotomy, together with other differences between STEMI and UA/NSTEMI (13), has been reflected since 2000 in separate practice guidelines. Despite these differences, more remains in common than distinct, including the discovery that atherothrombosis is an active, inflammatory process (947,948). Further inquiry has led to the concept of the vulnerable plaque and the vulnerable patient (949,950).

Whereas the incidence and risk of STEMI have decreased over the past 25 years, the relative frequency of UA/NSTEMI has increased, and its risk has remained relatively high (now comparable to that of STEMI) (951). Hence, improving UA/NSTEMI outcomes remains a challenge for the future.

A contemporary multinational observational study has emphasized the benefits of applying evidence-based guidelines in clinical practice (951a). Between 1999 and 2006, 27,558 patients with UA/NSTEMI in 14 countries were enrolled and followed for 6 months after discharge. Increases over the 7 years of enrollment were observed in the use of interventional therapy and of major pharmacological therapies, including beta blockers, statins, ACE inhibitors (or ARBs), low molecular weight heparin, GP IIb/IIa inhibitors, and thienopyridines. These changes were accompanied by marked declines (by one half) in in-hospital rates of heart failure or cardiogenic shock and recurrent MI and in 6-month rates of death (from 4.9% to 3.3%) and stroke (1.4% to 0.7%). Improved outcomes occurred despite an increase in patient risk profile. The future should emphasize further improvements in evidence-based guideline applications.

Improving prehospital and ED assessment should aim at more efficient entry into the health care system (e.g., limiting delays for NTG-refractory angina before calling 9-1-1), diagnosis and risk stratification (e.g., using marker changes while they are still in the normal range; in the future, with the aid of nontraditional biomarkers), and initiation of therapy. The future will see the increasing use of new imaging tests to assess the chest pain patient. By simultaneously assessing cardiac function, perfusion, and viability, CMR can yield a high sensitivity and specificity for diagnosis of CAD/ACS (296). Multislice cardiac computed tomography, which combines coronary calcium scoring with noninvasive coronary angiography (current resolution 0.5mm), has undergone favorable initial evaluation for assessment of the low- to intermediate-risk chest pain patient (297). The current status and appropriate application of CMR and cardiac CT are addressed in recent ACC/AHA documents (25,294).

The concept of a network of "heart attack centers" has been proposed as a way to improve MI care in the future (952–954). These heart attack centers would be organized and certified to provide the highest levels of care and would be geographically readily accessible to virtually all patients.

For high-risk patients, the concept of establishing and maintaining normal levels of myocardial perfusion mechanically continues to gain support, with evidence favoring intervention at even shorter (e.g., less than 6 to 24 h) rather than longer (i.e., greater than 48 to 96 h) intervals (540). The future should bring additional important information on this issue.

In contrast, for low-risk patients, evidence is growing that an initially noninvasive approach may be preferred (e.g., PCI shows benefit in high-risk women, as in men, but carries adverse risk potential in low-risk women) (532,565). This dependence of therapeutic benefit on disease risk has also been shown for antiplatelet and anticoagulant therapies. Hence, there is an increasing need to optimally stratify risk; some progress has been made (e.g., with the use of biomarkers integrated into an overall clinical risk score; see Section 2.2), but further development of risk assessment algorithms will be welcome in the future.

Platelets play a critical role UA/NSTEMI, and antiplatelet therapy continues to undergo testing. Higher (e.g., 600 mg or more of clopidogrel) and earlier loading doses of oral thienopyridine have been tested since the previous guidelines were published (see Section 3.2), with evidence of earlier antiplatelet activity. However, an incremental benefit of triple-antiplatelet therapy (ASA, GP IIb/ IIIa inhibitor, and clopidogrel) over double therapy with clopidogrel plus ASA (without GP IIb/IIIa inhibition) was recently shown for PCI in the setting of UA/NSTEMI (244).

Late thrombosis of DES (400,402,403,955), associated with delayed endothelialization (399,399a), recently has emerged as a therapeutic issue (401). Thus, longer periods of dual-antiplatelet therapy (i.e., at least 1 year) increasingly are advocated (see Section 3.2). Missing is an individualized approach to antiplatelet management: the future should bring efficient, validated platelet function testing to allow titration of the type, intensity, and duration of antiplatelet therapy. More choices in antiplatelet therapy can be expected, including intravenously administered and rapidly acting ADP receptor antagonists and more potent and/or more readily reversible oral agents. Biocompatible stents can also be expected looking forward, including biodegradable stents.

Triple-anticoagulant therapy (e.g., ASA, a thienopyridine, and warfarin) increasingly has a potential indication (e.g., PCI plus atrial fibrillation, cardiac or vascular thrombosis, or mechanical heart valve). Its current Class IIb recommendation (to be used "with caution" [1,2]; Fig. 11) is in need of a firmer evidence base (1,2).

Anticoagulant choices have proliferated since the last guidelines were published. Although LMWH (e.g., enoxaparin) gained recognition as an alternative or preferred anticoagulant in the previous guidelines, subsequent study in the setting of an early PCI strategy has suggested that either UFH or LWMH is acceptable (423). Meanwhile, agents from 2 new classes have been tested favorably (see Section 3.2) (424,425). Fondaparinux, a synthetic factor Xa inhibitor, was noninferior to enoxaparin at 9 d, with a lower bleeding risk. However, catheter-related thrombosis with fondaparinux raises concerns about its use with PCI, a concern amplified by its failure with PCI in STEMI (433). In contrast, fondaparinux is an appealing choice with a noninvasive approach to UA/NSTEMI, especially in those at higher risk of bleeding.

The ACUITY study, which tested bivalirudin for UA/NSTEMI, has led to a guidelines change to allow bivalirudin as an anticoagulant option (425). Bivalirudin was found to be noninferior to UFH/LMWH when given with a GP IIb/IIIa inhibitor. When given without a GP inhibitor, bleeding rates were lower but ischemic risk was higher unless clopidogrel therapy had been given before the procedure. Bivalirudin use was not tested with a conservative strategy. These guidelines present several options for anticoagulant/antiplatelet regimens, but whether there are clear preferences must await additional analysis and an enriched evidence base and could vary depending on the health care setting, the preferred treatment strategy (e.g., invasive vs. conservative), and individual patient factors.

This guideline revision recognizes ongoing developments in prevention (see Section 5.1.1). More aggressive LDL-C lowering (i.e., to the optimal LDL-C goal of less than 70 mg per dL) further reduces cardiovascular events, although an incremental mortality benefit remains to be shown (956). An additional tool for smoking cessation has appeared (varenicline), and others are in testing (see Section 5.2). High compliance with recommended secondary prevention measures has been shown to improve outcomes, but optimal compliance is still lacking, including at hospitals peer-rated as top tier (957). The evidence base for therapeutic lifestyle change continues to grow; the challenge for the future is more successful implementation (see Section 5.2).

Primary prevention remains a major challenge. Risk is currently assessed by traditional factors (e.g., Framingham risk score) and the intensity of treatment by risk score-determined goals. The majority of coronary events occur in a large segment of the population whose risk is intermediate (neither very low nor very high). Routine individual screening for asymptomatic disease is widely accepted for common cancers (e.g., colon and breast cancer) but not for atherosclerosis. Application of an "atherosclerosis test" (e.g., coronary artery calcium scoring or carotid intima-media thickness assessment) to middle-aged adults at intermediate risk has been proposed (25,294,949,950). The future will determine how broadly extended primary screening will be accepted to identify the "ACS-vulnerable" patient.

Progress in UA/NSTEMI remains uneven, with rapid evolution in some areas but slow progress in others. Our hope is that guidelines increasingly become based on levels of evidence A (or B). Writing these guidelines has highlighted the many holes in the fabric of the current evidence base. Academia, regulatory agencies, practicing physicians, professional organizations, and patient advocacy groups, as well as industry, must cooperate to achieve the universal goal of a fully evidence-based management strategy for UA/NSTEMI in the future. Strategies must include not only innovations in diagnosis and treatment but also fresh approaches to motivating lifestyle changes, leading to improved diet, weight control, physical activity, and tobacco avoidance, as well as to better compliance with evidence-based medical therapies (380).

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APPENDIX 1. RELATIONSHIPS WITH INDUSTRY—ACC/AHA COMMITTEE TO REVISE THE 2002 GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH UNSTABLE ANGINA/NON–ST-ELEVATION MYOCARDIAL INFARCTION

Committee Member	Research Grant	Speaker's Bureau	Stock Ownership	Consultant/Advisory Member
Cynthia D. Adams	None	• GlaxoSmithKline • Guidant • Medtronic • Pfizer	None	• CHF Technologies
Jeffery L. Anderson	• AstraZeneca • Bristol-Myers Squibb	• Merck*		• Bristol-Myers Squibb • Merck* • Sanofi • ThromboVision
Elliott M. Antman	• Accumetrics • Amgen, Inc. • AstraZeneca • Bayer Healthcare LLC • Biosite • Boehringer Mannheim • Beckman Coulter, Inc. • Bristol-Myers Squibb • Centocor • CV Therapeutics • Dade • Dendrion • Eli Lilly* • Genetech • GlaxoSmithKline • Inotek Pharmaceuticals Corp. • Integrated Therapeutics Corp. • Merck • Millennium* • Novartis Pharmaceuticals • Nuvelo, Inc. • Ortho-Clinical Diagnostics, Inc. • Pfizer, Inc. • Roche Diagnostics GmbH • Sanofi-Aventis Research Institute • Sanofi-Synthelabo Recherche • Schering-Plough • Sunoz Molecular • The National Institutes of Health	None	None	• Eli Lilly • Sanofi-Aventis
Charles R. Bridges	• None	None	None	None
Robert M. Califf	• Abbott Laboratories • Abbott Vascular Devices • Acorn Cardiovascular • Actelion • Acushphere, Inc. • Advanced CV Systems • Advanced Stent Tech • Agilent Technologies • Ajinomoto • Alexion • Allergan • Alsius • Amgen • Amylin Pharmaceuticals Inc. • Anadys • ANGES MG, Inc. • Argionx Pharmeceuticals • Ark Therapeutics, Ltd. • AstraZeneca • Aventis	• Bristol-Myers Squibb • Conceptis • Guilford Pharmaceuticals • Novartis Pharmaceutical • Pfizer • Sanofi-Aventis • Schering-Plough • The Medicines Company • Yamanouchi	• NITROX	• Conceptis

APPENDIX 1. Continued

Committee Member	Research Grant	Speaker's Bureau	Stock Ownership	Consultant/Advisory Member
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APPENDIX 1. Continued

Committee Member	Research Grant	Speaker's Bureau	Stock Ownership	Consultant/Advisory Member
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APPENDIX 1. Continued

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Robert M. Califf (continued)	• Suneis • Synaptic • Synthetic Blood International • Terumo Corp • The Medicines Company • Theravance • TherOx, Inc. • Titan Pharmaceuticals, Inc. • Valeant Pharmaceuticals • Valentis, Inc. • Velocimed • Veridex • Vertex Pharmaceuticals • VIASYS Healthcare, Inc. • Vicuron Pharmaceutical • Wyeth-Ayerst • XOMA • Xsira Pharmaceuticals • XTL Biopharmaceuticals • Xylum • Yamanouchi			
Donald E. Casey, Jr.	None	None	• Johnson & Johnson • Merck • Pfizer	None
William E. Chavey II	None	• NitroMed	None	None
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Judith S. Hochman	• Arginox Pharmaceuticals • CV Therapeutics • Eli Lilly • Millennium • Proctor & Gamble • Sanofi-Aventis	• Network for Continuing Medical Education (supported by Bristol-Myers Squibb/Sanofi)	None	• Datascope • Eli Lilly • GlaxoSmithKline • Merck • Schering-Plough
Thomas N. Levin	None	• Bristol-Myers Squibb/Sanofi • Foxhollow • Schering-Plough	• Boston ScientificFoxhollow • Johnson & Johnson • Medtronic • Pfizer	None

APPENDIX 1. Continued

Committee Member	Research Grant	Speaker's Bureau	Stock Ownership	Consultant/Advisory Member
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Eric D. Peterson	• Bristol-Myers Squibb/Sanofi • Millennium Pharmaceuticals • Schering-Plough	• Millennium Pharmaceuticals • Schering-Plough	None	None
Pierre Theroux	• AstraZeneca • Sanofi-Aventis	None	• AstraZeneca • Boston Scientific • Cardiovascular Therapeutics • Medtronic • Merck • Proctor & Gamble • Sanofii-Aventis	• AstraZeneca • Proctor & Gamble • Sanofi-Aventis
Nanette Kass Wenger	• Pfizer	• Bristol-Myers Squibb • CV Therapeutics • Eli Lilly • Merck • NitroMed • Novartis • Pfizer	None	• Abbott • AstraZeneca AB • Bristol-Myers Squibb • CV Therapeutics* • GlaxoSmithKline • NitroMed Heart Failure Advisory Board • Sanofi-Aventis • Schering-Plough
R. Scott Wright	• Centocor*	None	None	• Merck/Schering-Plough • Novartis • Pfizer

This table represents the actual or potential relationships with industry that were reported as of February 13, 2007. This table was updated in conjunction with all meetings and conference calls of the writing committee. *Indicates significant (greater than $10,000) relationship.

APPENDIX 2. RELATIONSHIPS WITH INDUSTRY—EXTERNAL PEER REVIEW FOR THE ACC/AHA COMMITTEE TO REVISE THE 2002 GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH UNSTABLE ANGINA/ NON–ST-ELEVATION MYOCARDIAL INFARCTION

Peer Reviewer*	Representation	Consulting Fees/ Honoraria	Speaker's Bureau	Ownership/ Partnership/ Principal	Research Grants	Salary
Eugene Braunwald	• Official	• AstraZeneca • Bayer Healthcare • Merck and Co. • Pfizer • Sanofi-Aventis • Schering-Plough • Dailchi Sankyo • Momenta • Scios†	None	None	• Accumetrics, Inc.† • AstraZeneca† • Bayer Healthcare† • Beckman Coulter† • Bristol-Myers Squibb† • CV Therapeutics† • Eli Lilly† • Inotek Pharmaceuticals† • Johnson & Johnson† • Merck and Co.† • National Institutes of Health† • Novartis† • Nuucid† • Pfizer† • Roche Diagnostics† • Sanofi-Aventis† • Schering-Plough†	None
Bernard Gersh	• Official–AHA	• Abbott • Asnorcylce Inc. • AstraZeneca • Boston Scientific • Bristol-Myers Squibb • Cardiovascular Therapeutics†	None	None	None	None
Chris Granger	• Official–AHA	• AstraZeneca† • GlaxoSmithKline† • Medicores Co. • Sanofi-Aventis†	None	None	• Alexion† • AstraZeneca† • Berlex† • Boehringer Ingelheim† • Bristol-Myers Squibb† • Genentech† • GlaxoSmithKline† • Novartis† • Proctor & Gamble† • Sanofi-Aventis†	None
David Holmes	• Official–ACC Board of Trustees	None	None	None	None	None
Kristen Newby	• Official–AHA	• Biosite • CV Therapeutics • Eli Lilly • Inverness Medical • Proctor & Gamble	• Bristol-Myers Squibb/Sanofi	None	• Bristol-Myers Squibb/ Sanofi† • Millennium Pharmaceuticals† • Roche Diagnostics† • Schering-Plough†	None
Rick Nishimura	• Official–ACC Lead Task Force Reviewer	None	None	None	None	None
Eugene Sherman	• Official–ACC Board of Governors	None	• Abbott • GlaxoSmithKline • Novartis • Sanofi-Aventis • Takeba	• General Electric† • Johnson & Johnson† • Pfizer†		

APPENDIX 2. Continued

Peer Reviewer*	Representation	Consulting Fees/ Honoraria	Speaker's Bureau	Ownership/ Partnership/ Principal	Research Grants	Salary
William Brady	• Organizational–American College of Emergency Physicians	• Heartscape • Medicolegal Review	None	None	None	None
Deborah Diercks	• Organizational–American College of Emergency Physicians	• Astellas • Inovise Technology • Medicines Company • Sanofi-Aventis†	• Bristol-Myers Squibb • Sanofi-Aventis† • Schering-Plough	None	• The Medicines Company	None
Lakshimi Halasyamani	• Organizational–American College of Physicians‡	None	None	None	None	None
Robert Higgins	• Organizational–Society of Thoracic Surgeons‡	None	None	None	None	None
Morton Kern	• Organizational–Society for Cardiovascular Angiography and Interventions and ACC/AHA/SCAI PCI Guidelines Writing Committee‡	• Merrit Medical • Therox, Inc.	None	None	None	None
Marjorie King	• Organizational–American Association of Cardiovascular and Pulmonary Rehabilitation‡	None	None	None	None	None
Michael Lim	• Organizational–Society for Cardiovascular Angiography and Interventions‡	None	• Bristol-Myers Squibb • Merck • Sanofi-Aventis	None	None	None
Walter Merrill	• Organizational–Society of Thoracic Surgeons‡	None	None	None	None	None
Charles Pollack	• Organizational–Society for Academic Emergency Medicine‡	• Bristol-Myers Squibb • Sanofi-Aventis • Schering-Plough • The Medicines Company	• Sanofi-Aventis • Schering-Plough	None	• GlaxoSmithKline†	• Spouse employed by The Medicines Company†
Mazen Abu-Fadel	• Content–ACCF Cardiac Catheterization and Intervention Committee	None	None	None	None	None

APPENDIX 2. Continued

Peer Reviewer*	Representation	Consulting Fees/ Honoraria	Speaker's Bureau	Ownership/ Partnership/ Principal	Research Grants	Salary
Paul Armstrong	• Content–ACC/ AHA STEMI Guidelines Writing Committee	• Abbott Laboratories • ArgiNOx • Boehringer Ingelheim • Hoffmann LaRoche Canada • Sanofi-Aventis • TarGen	None		• Boehringer Ingelheim† • Hoffmann LaRoche Canada† • Proctor & Gamble/Alexion† • Sanofi-Aventis†	• Medicure†
Eric Bates	• Content–ACC/ AHA STEMI Guidelines Writing Committee	• AstraZeneca • Eli Lilly • GlaxoSmithKline • Sanofi-Aventis • Schering-Plough	None	None	• Eli Lilly	None
Alexander Battler	• Content–ACC/ AHA Acute Coronary Syndromes Data Standards Writing Committee	None	None	None	None	None
Vera Bittner	• Content–ACCF Prevention of Cardiovascular Disease Committee	• CV Therapeutics • Pfizer • Reliant	None	None	• Atherogenics† • NHLBI† • Pfizer†	None
Christopher Cannon	• Content–ACC/ AHA Acute Coronary Syndromes Data Standards Writing Committee	• AstraZeneca† • BGB New York • Bristol-Myers Squibb† • DIME • GlaxoSmithKline† • Merck† • NCME • Pfizer† • Sanofi-Aventis† • Schering-Plough†	• Accumetrics† • AstraZeneca† • Bristol-Myers Squibb† • Merck† • Pfizer† • Sanofi-Aventis† • Schering-Plough†	None	• Accumetrics† • Amgen • AstraZeneca† • Bayer Healthcare • Beckman Coulter, Inc. • Biosite Inc. • Bristol-Myers Squibb Pharmaceutical Research Inst. • CV Therapeutics • Eli Lilly • GlaxoSmithKline • Inotek Pharmaceuticals • Integrated Therapeutics Corp. • Merck† • Millenium Pharmaceuticals Inc. • Novartis Pharmaceuticals • Nuvelo, Inc. • Ortho-Clinical Diagnostics • Pfizer • Roche Diagnostics • Sanofi-Aventis • Sanofi-Synthelabo Recherche • Schering-Plough† • The National Institutes of Health	None
Bernard Chaitman	• Content–ACC/ AHA Acute Coronary Syndromes Data Standards Writing Committee	• Merck† • CV Therapeutics†	• Pfizer†	None	• CV Therapeutics†	None

APPENDIX 2. Continued

Peer Reviewer*	Representation	Consulting Fees/ Honoraria	Speaker's Bureau	Ownership/ Partnership/ Principal	Research Grants	Salary
Jose Diez	• Content–ACCF Cardiac Catheterization and Intervention Committee	• Sanofi-Aventis	None	None	None	None
Stephen Ellis	• Content–ACC/ AHA Acute Coronary Syndromes Data Standards Writing Committee	• Abbott • Boston Scientific • Cordis • Viacor	None	None	• Centocor	None
James Ferguson	• Content–ACCF Cardiac Catheterization and Intervention Committee	• Bristol-Myers Squibb • Eisai† • GlaxoSmithKline • Prism • Sanofi-Aventis† • Schering-Plough • Takeda • The Medicus Co. • Therox	• Bristol-Myers Squibb • Sanofi-Aventis† • Schering-Plough	None	• Eisai • The Medicus Co. • Vitatron/Medtronic	None
Gregg Fonarow	• Content–ACCF Prevention of Cardiovascular Disease Committee	• AstraZeneca • Bristol-Myers Squibb/ Sanofi† • GlaxoSmithKline† • Guidant • Medtronic† • Merck/Schering-Plough† • Pfizer† • St. Judes	• AstraZeneca • Bristol-Myers Squibb/Sanofi† • GlaxoSmithKline† • Medtronic† • Merck/Schering-Plough† • Pfizer†	None	• Guidant • Medtronic† • Pfizer† • St. Judes	None
Robert Harrington	• Content–ACC/ AHA Acute Coronary Syndromes Data Standards Writing Committee	None	None	None	• AstraZeneca† • Bristol-Myers Squibb† • Lilly† • JMC† • Merck† • Sanofi-Aventis† • Schering-Plough†	None
Edward Havranek	• Content–ACC/ AHA Task Force on Data Standards	• CV Therapeutics • McKesson	None	None	None	None
Harlan Krumholz	• Content–ACC/ AHA STEMI Guidelines Writing Committee, ACC/AHA Acute Coronary Syndromes Data Standards Writing Committee	• CV Therapeutics • United Healthcare†	None	None	None	None
Janet Long	• Content–ACCF Prevention of Cardiovascular Disease Committee	None	• AstraZeneca	None	None	None

APPENDIX 2. Continued

Peer Reviewer*	Representation	Consulting Fees/ Honoraria	Speaker's Bureau	Ownership/ Partnership/ Principal	Research Grants	Salary
C. Noel Bairey Merz	• Content	• AstraZeneca • Bayer† • KOS • Merck • Pfizer	None	• Eli Lilly† • Johnson & Johnson† • Medtronic†	• Merck • Pfizer†	None
Debabrata Mukherjee	• Content–ACCF Cardiac Catheterization and Intervention Committee	None	None	None	None	None
Charles Mullany	• Content–ACC/AHA STEMI Guidelines Writing Committee	None	None	None	• AstraZeneca • Atricure • Avant Immunotherapeutics • Baxter • Carbomedics/Sorin Group • CryoLife • Jarvik Heart • Medtronic • St. Jude Medical • Thoratec Corporation • TransTech Pharma • W.L. Gore and Associates	None
Magnus Ohman	• Content–ESC Guidelines on Non–ST-Elevation Acute Coronary Syndromes Writing Committee	• Inovise† • Liposcience • Response Biomedical • Savacor† • The Medicines Company	None	• Inovise† • Medtronic† • Savacor†	• Berlex† • Bristol-Myers Squibb† • Eli Lilly† • Millenium Pharmaceuticals† • Sanofi-Aventis† • Schering-Plough†	None
Joseph Ornato	• Content–ACC/AHA STEMI Guidelines Writing Committee	• Boehringer Ingelheim • Bristol-Myers Squibb • Genetech • PDL BioPharma, Inc. • ZOLL	None	None	None	None
Rita Redberg	• Content–ACCF Prevention of Cardiovascular Disease Committee	None	None	None	None	None
Charanjit Rihal	• Content–ACCF Cardiac Catheterization and Intervention Committee	None	None	None	None	None
David Williams	• Content–ACC/AHA/SCAI PCI Guidelines Writing Committee	• Abbott • Cordis†	None	None	• Cordis Guidant	None
Kim Williams	• Content–ACCF Cardiovascular Imaging Committee	• CV Therapeutics† • GE Healthcare† • King Pharmaceuticals†	• Astellas Healthcare† • GE Healthcare†	None	• Bristol-Myers Squibb† • CV Therapeutics† • GE Healthcare† • Molecular Insight Pharmaceuticals†	

This table represents the relationships of peer reviewers with industry that were disclosed at the time of peer review of this guideline. It does not necessarily reflect relationships with industry at the time of publication. *Names are listed in alphabetical order within each category of review. †Indicates a significant relationship (valued at $10,000 or more). ‡Participation in the peer review process does not imply endorsement of this document.

APPENDIX 3. ABBREVIATIONS

AAFP	American Academy of Family Physicians
ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ACE	angiotensin converting enzyme
ACEP	American College of Emergency Physicians
ACP	American College of Physicians
ACS	acute coronary syndrome
ACT	activated clotting time
ACUITY	Acute Catheterization and Urgent Intervention Triage strategy
AHA	American Heart Association
AMI	acute myocardial infarction
aPTT	activated partial thromboplastin time
ARTS	Arterial Revascularization Therapy Study
ASA	aspirin
AST, SGOT	aspartate aminotransferase
AV	atrioventricular
BARI	Bypass Angioplasty Revascularization Investigation
BNP	B-type natriuretic peptide
CABG	coronary artery bypass graft
CABRI	Coronary Angioplasty versus Bypass Revascularization Investigation
CAD	coronary artery disease
CAPTURE	c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina trial
CASS	Coronary Artery Surgery Study
CCB	calcium channel blocker
CCTA	coronary computed tomographic angiogram
CHD	coronary heart disease
CI	confidence interval
CKD	chronic kidney disease
CK-MB	creatine kinase-myocardial band
CMR	cardiac magnetic resonance
COMMIT	ClOpidogrel and Metoprolol in Myocardial Infarction Trial
COX	cyclooxygenase
CPR	cardiopulmonary resuscitation
CREDO	Clopidogrel for the Reduction of Events During Observation trial
CRP	C-reactive protein
CT	computed tomography
cTn	cardiac troponin
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events trial
CVD	cardiovascular disease
d	day
DAVIT	Danish Study Group on Verapamil in Myocardial Infarction
DES	drug-eluting stent
DIGAMI	Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction
ECG	electrocardiogram
ED	emergency department
EMS	emergency medical services
EPIC	Evaluation of c7E3 for the Prevention of Ischemic Complications
EPILOG	Evaluation of PTCA and Improve Long-term Outcome by c7E3 GP IIb/IIIa receptor blockade
EPISTENT	Evaluation of Platelet IIb/IIIa Inhibitor for STENTing
ERACI-II	Estudio Randomizado Argentino de Angioplastia vs. Cirugia-II
ESC	European Society of Cardiology
ESSENCE	Efficacy and Safety of Subcutaneous Enoxaparin in Unstable Angina and Non-Q Wave Myocaridal Infarction trial
FRIC	FRagmin In ustable Coronary artery disease
FRISC	Fast Revascularization During Instability in Coronary Artery Disease
FRISC-II	Fast Revascularization During Instability in Coronary Artery Disease-II

APPENDIX 3. Continued

GISSI	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto-1 1 trial
GISSI-3	Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico
GP	glycoprotein
GRACE	Global Registry of Acute Coronary Events
GUSTO	Global Utilization of Streptokinase and t-PA for Occluded Arteries
GUSTO-II	Global Use of Strategies to Open Occluded Coronary Arteries II
h	hour
Hb	hemoglobin
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
HOPE	Heart Outcomes Prevention Evaluation Study
HR	hazard ratio
IABP	intra-aortic balloon pump
ICTUS	Invasive versus Conservative Treatment in Unstable coronary Syndromes
ICU	intensive care unit
IPT	interpersonal psychotherapy
INR	international normalized ratio
ISAR-REACT	Intracoronary stenting and Antithrombotic Regimen- Rapid Early Action for Coronary Treatment
ISIS-2	Second International Study of Infarct Survival
ISIS-4	Fourth International Study of Infarct Survival
IU	international unit
IV	intravenous
JNC 7	Seventh Joint National Committee on High Blood Pressure
kg	kilogram
LAD	left anterior descending coronary artery
LDL-C	low-density lipoprotein choloesterol
LMWH	low-molecular-weight heparin
LV	left ventricular
LVEF	left ventricular ejection fraction
MASS II	Multicenter Anti Atherosclerotic Study II
MATE	Medicine versus Angiography in Thrombolytic Exclusion
MDPIT	Multicenter Diltiazem Postinfarction Trial
MDRD	Modification of Diet and Renal Disease
METS	metabolic equivalents
MI	myocardial infarction
MVO_2	myocardial oxygen demand
NCEP	National Cholesterol Education Program
NHLBI	National Heart, Lung, and Blood Institute
NS	nonsignificant
NSTEMI	non–ST-segment elevation myocardial infarction
NTG	nitroglycerin
NT-proBNP	N-terminal B-type natriuretic peptide
OASIS	Organization to Assess Strategies for Ischemic Syndromes
OR	odds ratio
PCI	percutaneous coronary intervention
PDA	personal digital assistant
PRISM	Platelet Receptor Inhibition in Ischemic Syndrome Management
PRISM-PLUS	Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms
PTCA	percutaneous transluminal coronary angioplasty
PURSUIT	Platelet Glycoprotein IIb/IIIa in Unstable 16 Angina: Receptor Suppression Using Integrilin Therapy
REACT	Rapid Early Action for Coronary Treatment
REPLACE-2	Randomized Evaluation of PCI Linking Angiomax to reduced Clinical Events
RITA	Research Group in Instability in Coronary Artery Disease trial
RR	risk ratio
SaO_2	arterial oxygen saturation
SC	subcutaneous

APPENDIX 3. Continued

SCAI	Society for Cardiovascular Angiography and Interventions
SHOCK	SHould we emergently revascularize Occluded Coronaries for cardiogenic shocK study
SoS	Stent or Surgery
STEMI	ST-elevation myocardial infarction
STS	Society of Thoracic Surgeons
SVG	saphenous vein graft
SYNERGY	Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors trial
TACTICS-TIMI 18	Treat Angina with Aggrastat and determine Cost of therapy with Invasive or Conservative Strategy (TACTICS) TIMI-18 trial
TARGET	Do Tirofiban and ReoPro Give Similar Efficacy Outcomes Trial
TIMI	Thrombolysis In Myocardial Infarction
TnI	troponin I
TnT	troponin T
U	units
UA	unstable angina
UA/NSTEMI	unstable angina/non–ST-elevation myocardial infarction
UFH	unfractionated heparin
VANQWISH	Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital
VINO	Value of first day angiography/angioplasty In evolving Non-ST-Segment elevation myocardial infarction: Open randomized trial
WISE	Women's Ischemia Syndrome Evaluation

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